

Cyanamid's Nitrogen Chemicals Digest

VOL. IV

THE CHEMISTRY OF GUANIDINE



AMERICAN Cyanamid COMPANY

30 ROCKEFELLER PLAZA

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SYNTHETIC ORGANIC CHEMICALS DEPARTMENT

FOREWORD

American Cyanamid Company has been interested in the chemistry of nitrogen from the day it was founded in 1907. Over the years a great deal of knowledge has been developed by Cyanamid and others on this subject. Some years ago a program was adopted of compiling and publishing technical data on the chemistry of nitrogen compounds. Much of this information is the result of research in the company's laboratories. This series, Cyanamid's Nitrogen Chemicals Digest, is continued this year with Volume IV THE CHEMISTRY OF GUANIDINE.

Heretofore the information on the chemistry and applications of guanidine and guanidine compounds while considerable has been widely scattered. Due to the increasing interest in Guanidine Chemistry, Volume IV has been published to make available for the first time, under one cover a complete and up-to-date treatise on this subject.

In making this booklet available to those active in Research and Development it is hoped that further uses for the Guanidines will be found. We shall be pleased to consult with you further about these chemicals if you will address your inquiries as follows—

AMERICAN *Cyanamid* COMPANY
SYNTHETIC ORGANIC CHEMICALS DEPARTMENT

January 1, 1950

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INTRODUCTION



Guanidine, H_2NCNH_2 , was discovered by Strecker (425) in 1861 in the course of his work on the constituents of guano. Since that time it has been found that guanidine is present as a part of a variety of other natural products, among which may be mentioned egg albumen, nucleic acids, streptomycin and folic acid.

Inasmuch as the guanidine structure is involved in a number of important synthetic pharmaceuticals, plastics, dyestuffs, and explosives and because of the reactivity of the molecule its value to the research chemist is great indeed. This booklet is written to call your attention to the variety of chemical syntheses which are possible with this versatile intermediate and to the great number of industrial uses which have already been found for various guanidine derivatives. It is hoped that this discussion will suggest to the reader new uses for guanidine and its salts.

The scope of this booklet has been purposely limited in an effort to emphasize only those aspects of guanidine chemistry which seem to be of greatest importance. American Cyanamid Company would welcome correspondence regarding details which have not been fully discussed and any other questions or problems which may arise regarding the chemistry of guanidine.

American Cyanamid Company has available samples of several guanidine salts for application to your research problems. Guanidine carbonate, nitrate and hydrochloride are available in commercial quantities. Guanidine stearate and the mono- and dihydrogen phosphate are offered in experimental amounts. Samples of diphenyl guanidine, di-(orthotolyl) guanidine, phenyl guanidine stearate and phenyl guanidine carbonate will be furnished upon request.

PHYSICAL PROPERTIES

Guanidine is a crystalline, monoacidic base of a strength nearly equivalent to that of sodium hydroxide (105, 181, 311). Although free guanidine is not commercially available at the present time, the American Cyanamid Company can supply several guanidine salts. Some of the physical properties of these salts are outlined in Table I. These properties were determined at the Stamford Laboratories of the American Cyanamid Company except where noted otherwise.

TABLE I
The Physical Properties of Some Guanidine Salts

Property	Guanidine Salt					
	Cl ⁻	NO ₃ ⁻	CO ₃ ⁼	H ₂ PO ₄ ⁻	HPO ₄ ⁼	C ₁₇ H ₃₅ CO ₂ ⁻
<i>Molecular Weight</i> (theory)	95.54	122.09	180.17	157.07	216.14	343.54
<i>Melting Point, °C.</i>						
Hot stage(a)	185-186.9	211.4-212.7		129.6-129.9		
Capillary tube	184	214.2	241		246	75.8-87.8
<i>Apparent Density, Solid,</i> 30°C. (± 0.004)	1.344	1.436	1.251	1.684	1.481	1.026
<i>Solubility</i>						
Water	Fig. 1	Fig. 1	Fig. 1	Fig. 1	Fig. 1	(b)
Ethanol, g./100 g. solvent 78°C.	Fig. 2	Fig. 2	<0.1	<0.1	<0.1	(c)
Acetone, g./100 g. solvent 30°C.	<0.05	<0.1	0.3(d)	<0.05	<0.05	<0.05
50°C.	<0.05	0.1(d)	0.3(d)	<0.05	<0.05	0.1(d)
Benzene, g./100 g. solvent 30°C.	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
60°C.	<0.05	<0.05	<0.05	<0.05	<0.05	>15
Hexane, g./100 g. solvent 30°C.-50°C.	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

NITROGEN CHEMICALS DIGEST

TABLE I—continued

Property	Guanidine Salt					
	Cl ⁻	NO ₃ ⁻	CO ₃ ⁼	H ₂ PO ₄ ⁻	HPO ₄ ⁼	C ₁₇ H ₃₅ CO ₂ ⁻
<i>Optical</i>						
Crystal System		(e)	(483)			
Crystal Habit	Equant to tabular	Equant	Tetragonal	Equant	Tetragonal	(g)
Refractive Indices	N _X 1.520 N _Y 1.590 N _Z 1.638	N _X 1.350 N _Y 1.575 N _Z 1.582	N _O 1.4963 N _E 1.4864	N _X 1.468 N _Y 1.570 N _Z 1.582	N _O 1.548 N _E 1.533	(g)
Birefringence	0.118	0.232	0.0099	0.114	0.015	(g)
Optic Sign	(-)	(-)	(-)	(-)	(-)	(g)
Optic Axial Angles				50°		
2E	160° (calc.)	20–27°				
2V	76° (calc.)	12–17°		36°		
<i>pH of Aqueous Solutions, 25°C.</i>						
4% by weight	6.4	5.7 (1%)	11.2	4.3	8.4	10
20% by weight	7.6	5.7 (10%)	11.3	3.9	8.1	
<i>Refractive Index of Aqueous Solutions, n_D²⁵</i>						
4% by weight	1.3409	1.3399	1.3410	1.3399	1.3403	(b)
20% by weight	1.3719	1.3558	1.3770	1.3651	1.3670	
<i>Vapor Pressure of Aqueous Solutions</i>						
	Fig. 3		Fig. 3	Fig. 3	Fig. 3	(b)
<i>Spectra</i>						
Infrared	(h)	(h)	Fig. 4	(h)	(h)	
Ultraviolet	(i)	(i)	(i)	(i)	(i)	(i)

(a) The equilibrium melting point was determined on the microscopic hot stage according to Kofler's procedure (6, 250).

(b) Guanidine stearate forms colloidal solutions at low concentration (<1%). The viscosity increases with increasing concentration until a semi-solid gel is formed.

(c) Guanidine stearate dissolves in absolute ethanol forming a hazy colloidal solution. The solubility is >60 g./100 g. solvent at 28°C.

(d) These values are only approximately correct (\pm 20%).

(e) Guanidine nitrate crystals are strained, as is indicated by the variability of the optic axial angles.

(f) The optical properties reported here are those of guanidine hydrogen phosphate monohydrate.

(g) Guanidine stearate crystals are small and show undulatory extinction. Their habit is such that measurement of the critical properties is not possible.

(h) These spectra are available upon request. See also reference 69.

(i) The guanidine salts show only weak absorption above 2100 Å except in the case of guanidine nitrate which absorbs strongly at 3000 Å. (See also reference 372).

NITROGEN CHEMICALS DIGEST

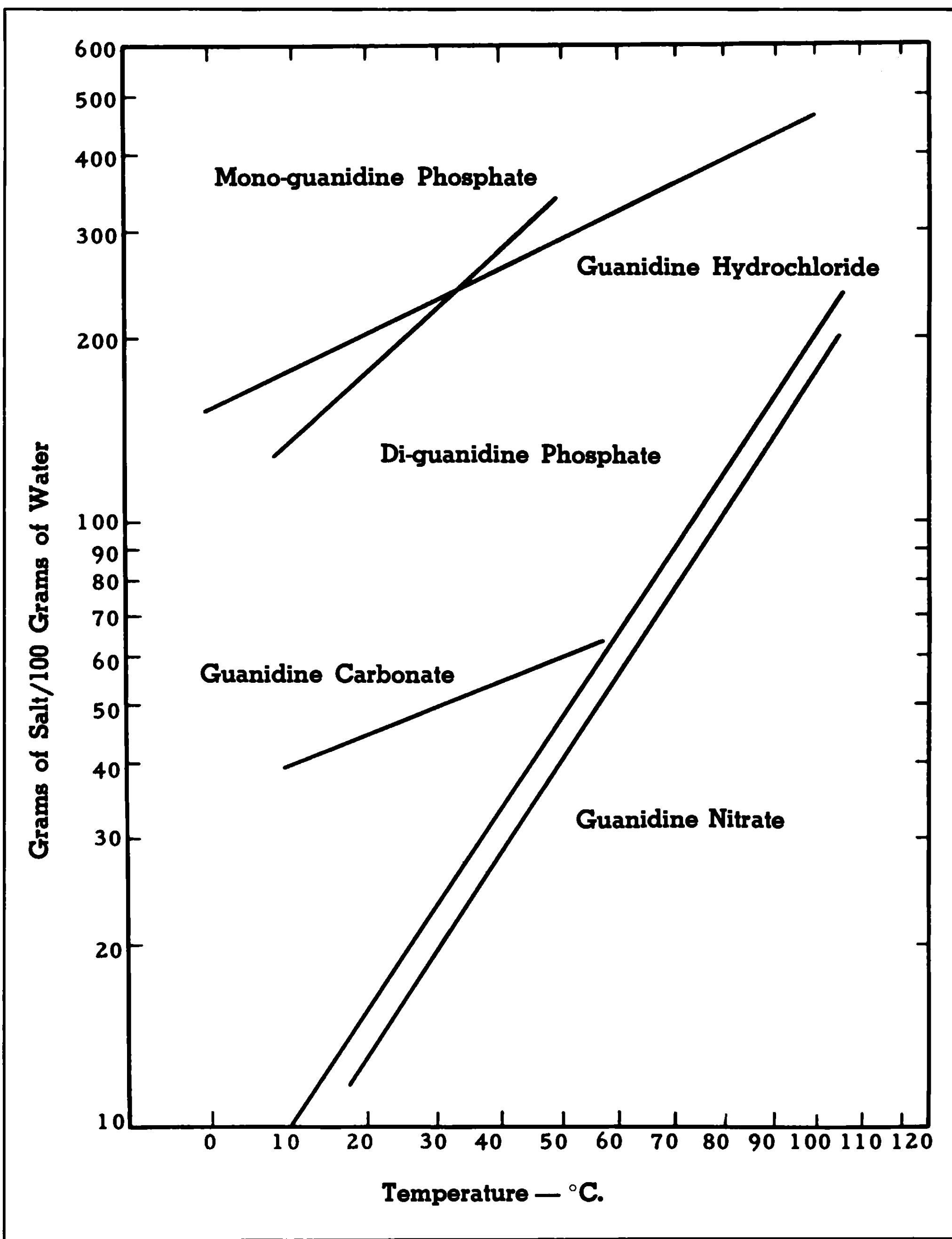


Figure 1—The Solubility of Various Guanidine Salts in Water at Several Temperatures

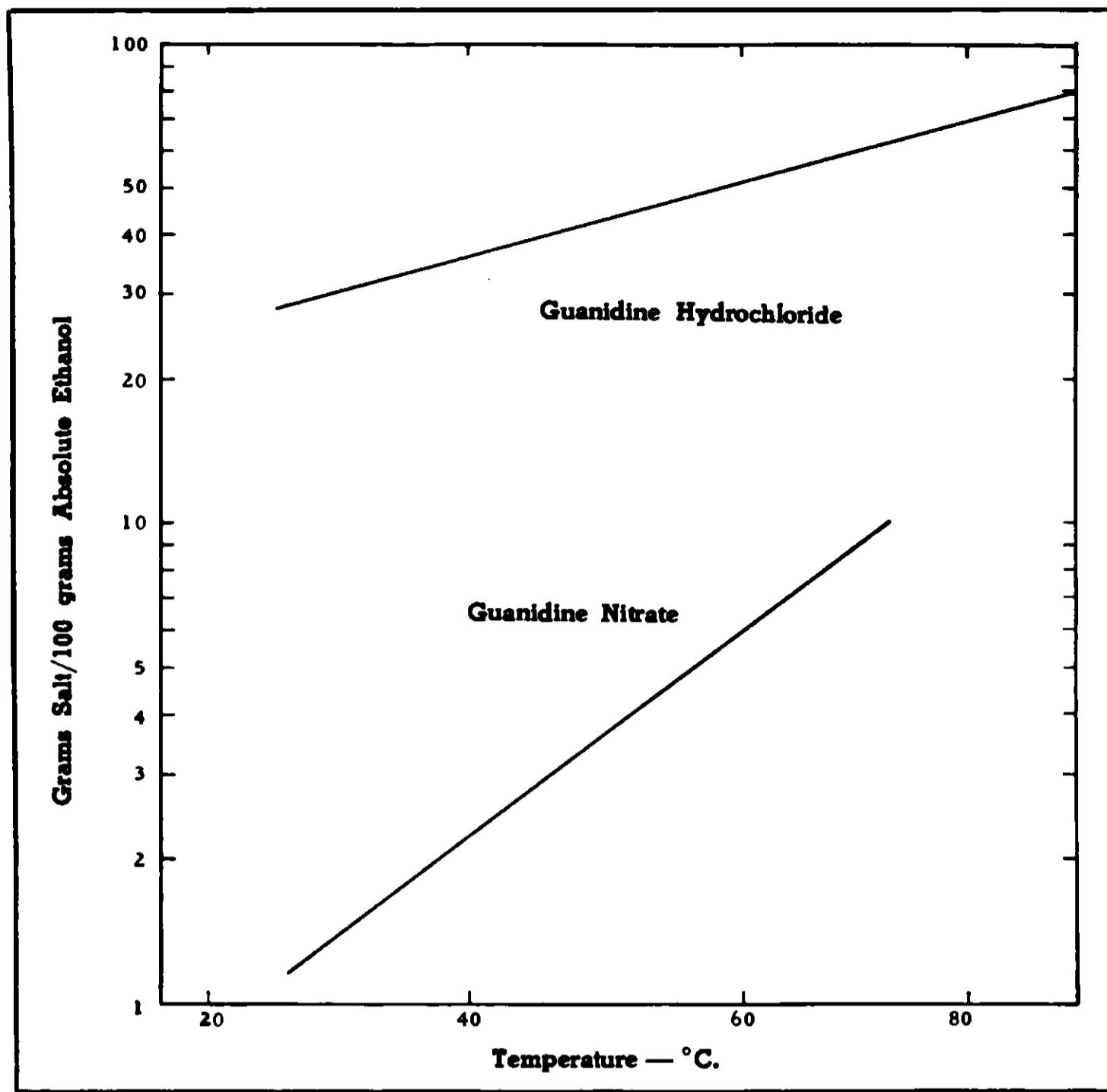


Figure 2—Solubility of Guanidine Salts in Absolute Ethanol

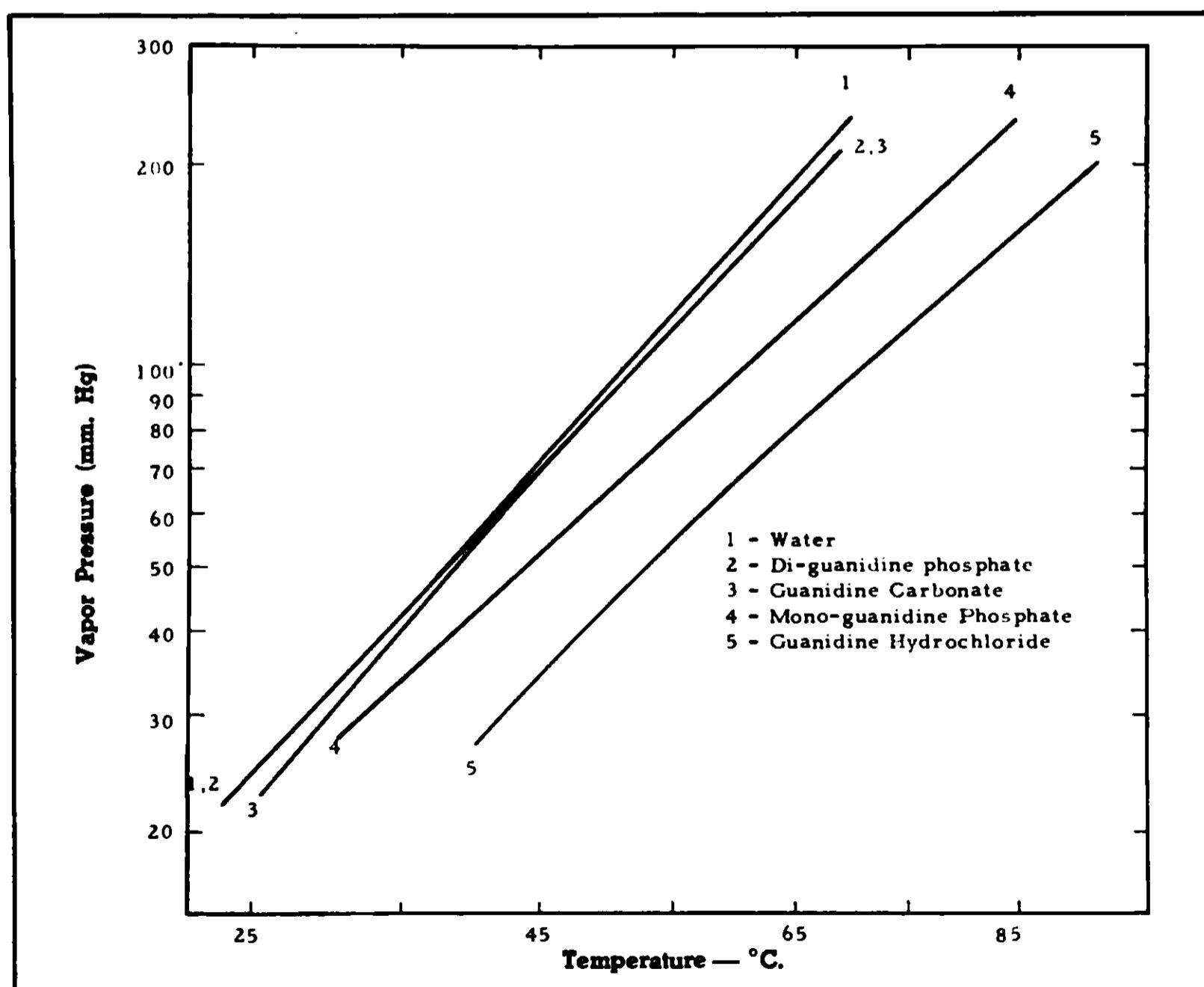


Figure 3—Vapor Pressures of Saturated Aqueous Solutions of Several Guanidine Salts at Different Temperatures

NITROGEN CHEMICALS DIGEST

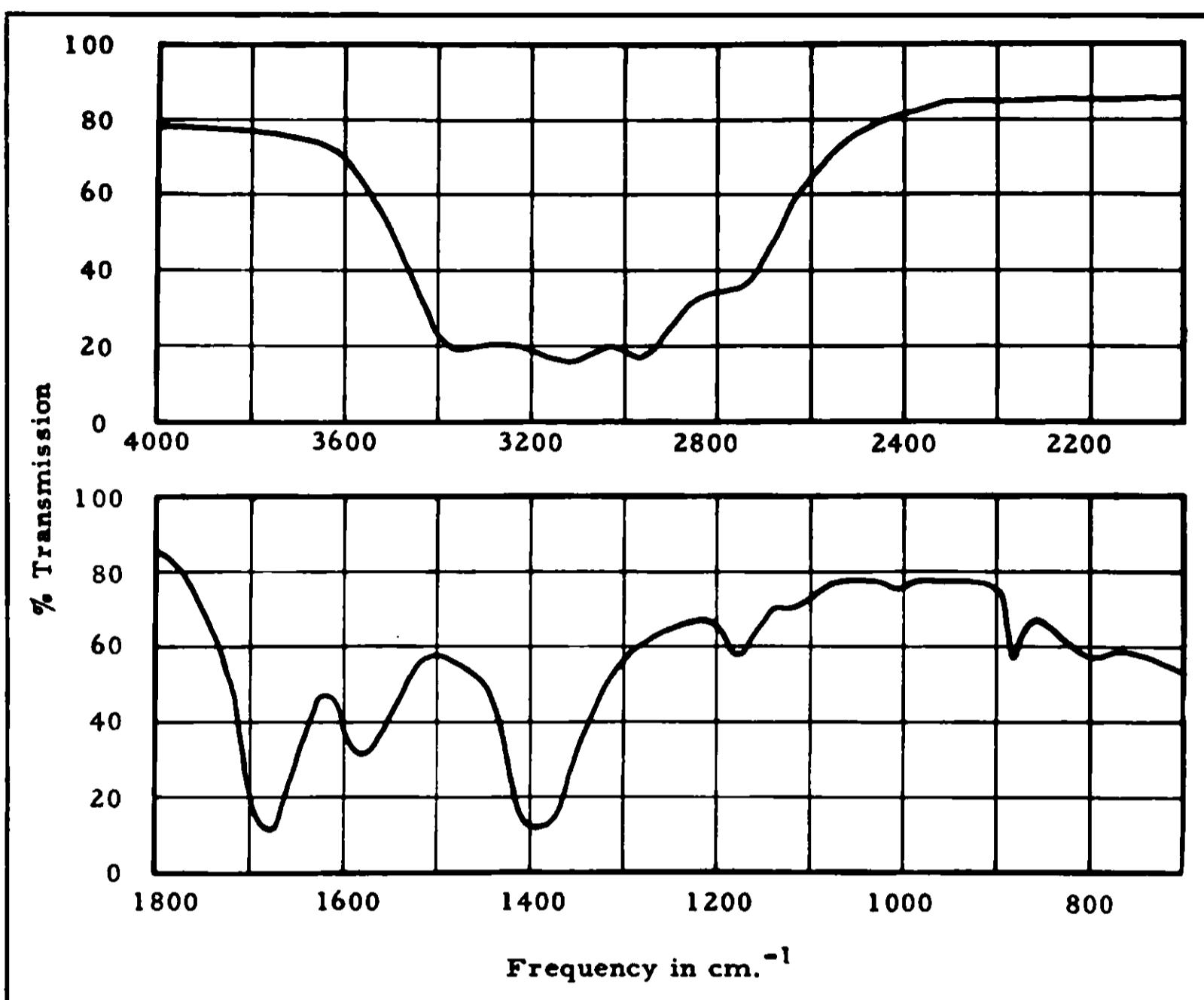


Figure 4—Infrared Absorption Spectrum of Guanidine Carbonate

Other physical properties of guanidine salts which have been studied include conductivity (155), magnetic susceptibility (23), magnetic anisotropy (22) crystal structure (66, 436), cryoscopic measurements (397), eutectics (462), polymorphic transitions (54) and the Raman spectra (11, 331, 369). The solubility of guanidine carbonate in various alcohol-water solutions is shown in Figure 5. The density of aqueous solutions of guanidine hydrochloride is illustrated in Figure 6.

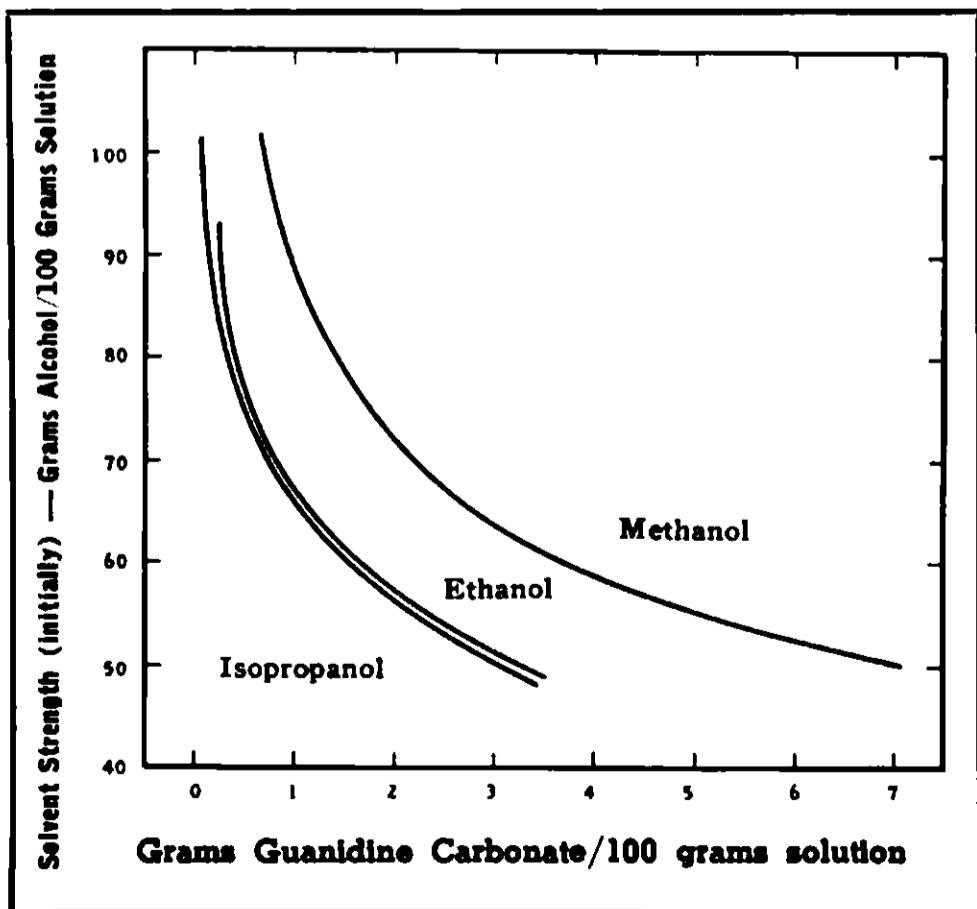


Figure 5—Solubility of Guanidine Carbonate in Several Alcohol-Water Systems at 23°C.

NITROGEN CHEMICALS DIGEST

Table II contains a summary of the thermodynamic properties of free guanidine and some of its salts.

TABLE II
The Thermodynamic Properties of Guanidine
and Some of Its Salts

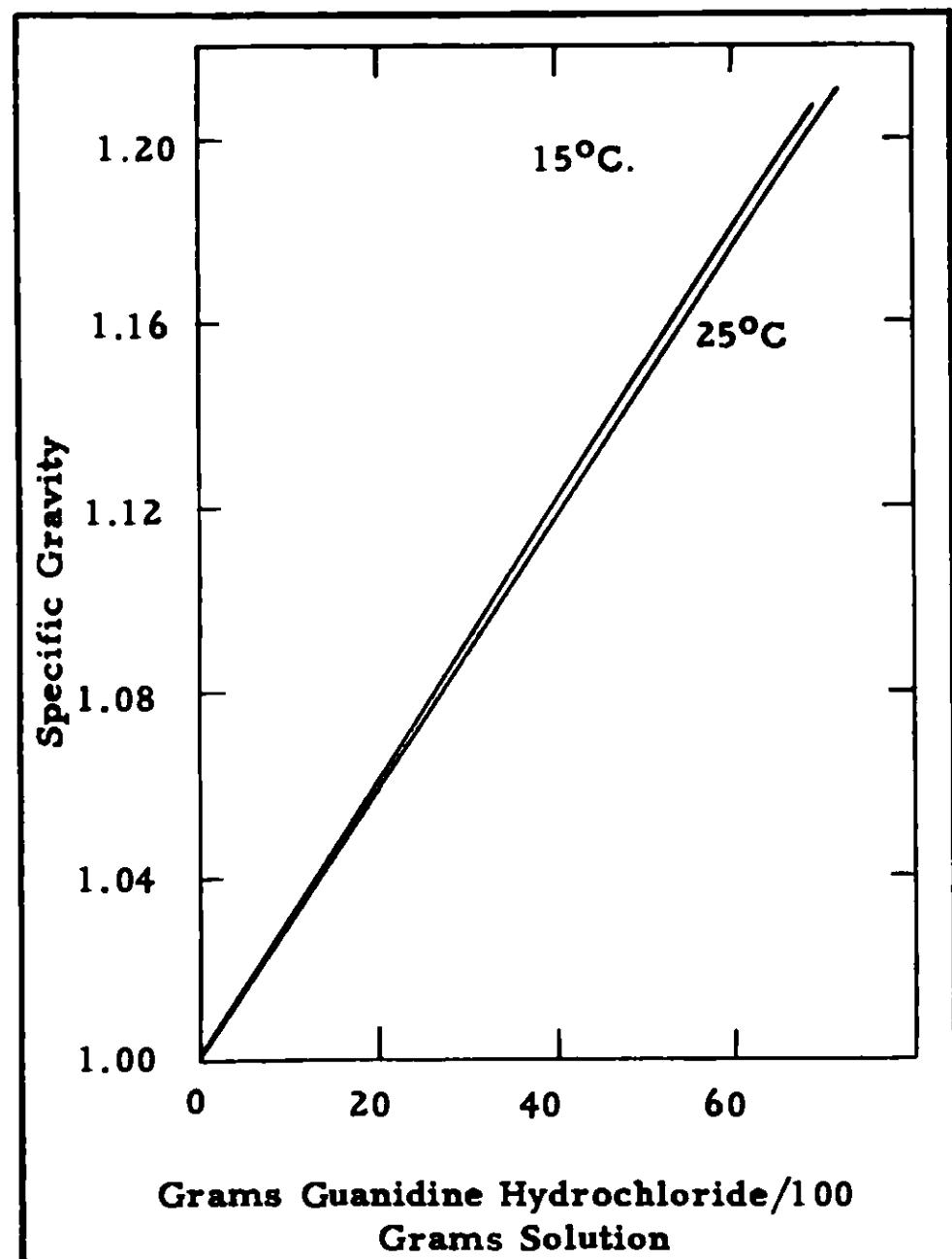


Figure 6—Specific Gravity of Aqueous Solutions of Guanidine Hydrochloride at Two Temperatures

<i>Heat of Formation</i>	$-\Delta H^\circ_{298}$, kcal./mole
Guanidine	13 (9)
Guanidine nitrate	92 (42)
Guanidine carbonate	232 (212)
<i>Heat of Combustion</i>	$-\Delta H_C$, kcal./mole
Guanidine	251 (9)
Guanidine nitrate	209.9 (290)
Guanidine carbonate	207.5 (42)
Guanidine carbonate	459.8 (212)
<i>Entropy</i>	S_{298} , Cal./deg./mole
Guanidine carbonate	70.6 (211)
<i>Entropy of Formation</i>	ΔS , Cal./deg./mole
Guanidine carbonate	-331.7 (212)
<i>Free Energy</i>	ΔF° , kcal./mole
Guanidine carbonate	-144.3 (212)
<i>Heat of Neutralization</i>	kcal./mole
Guanidine carbonate	14.1 (290)
<i>Heat of Solution</i>	kcal./mole
Guanidine nitrate	10.15 (42)
Guanidine hydrochloride	Fig. 7

Heat Capacity

Guanidine carbonate—Heat capacity data are recorded for the temperature range -183°C. to 25°C. (211).

Guanidine hydrochloride—Figure 7, page 9, shows the variation of specific heat with concentration of an aqueous solution at 20°C.

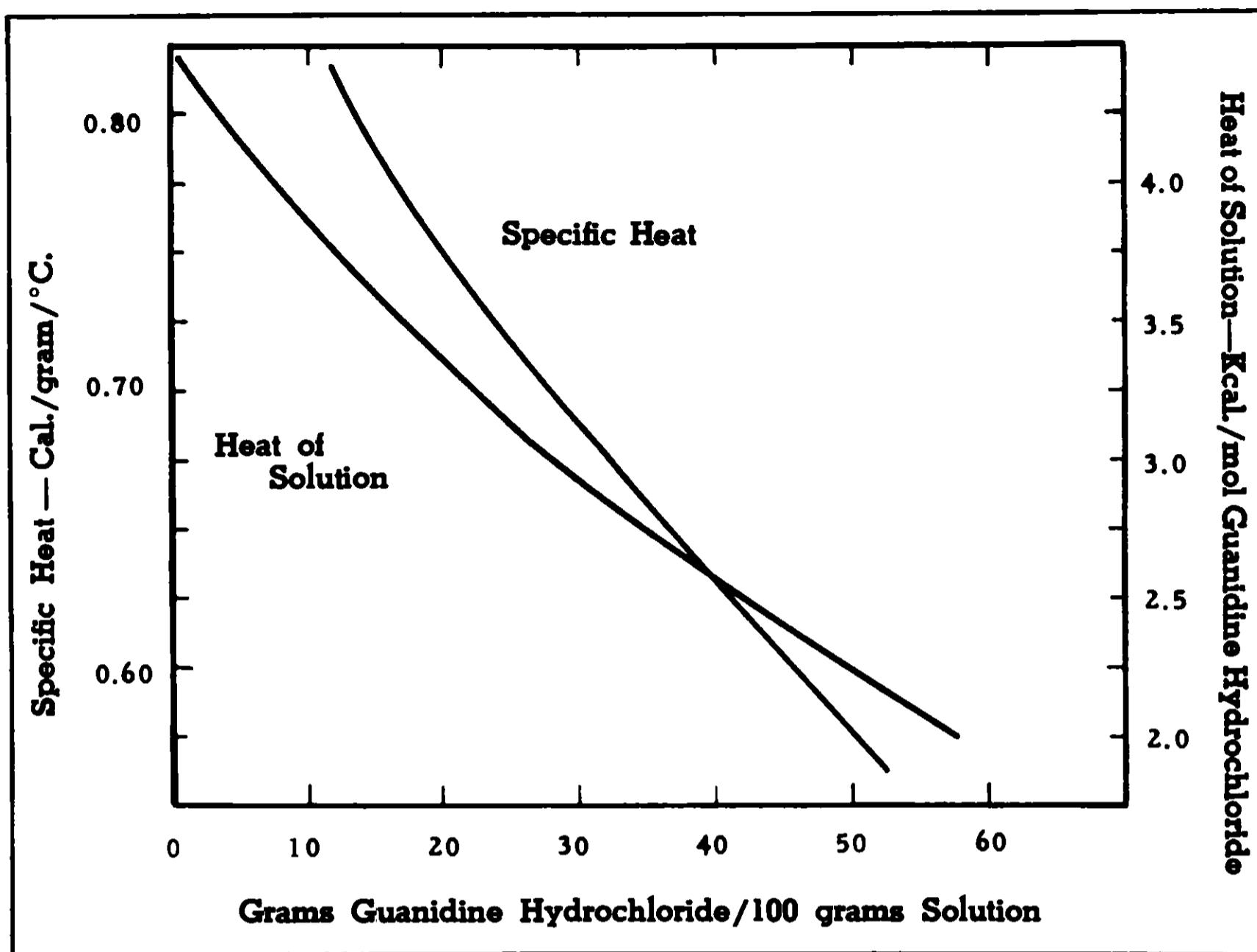


Figure 7—Specific Heat of Guanidine Hydrochloride and Heat of Solution of Guanidine Hydrochloride in water at 20°C.

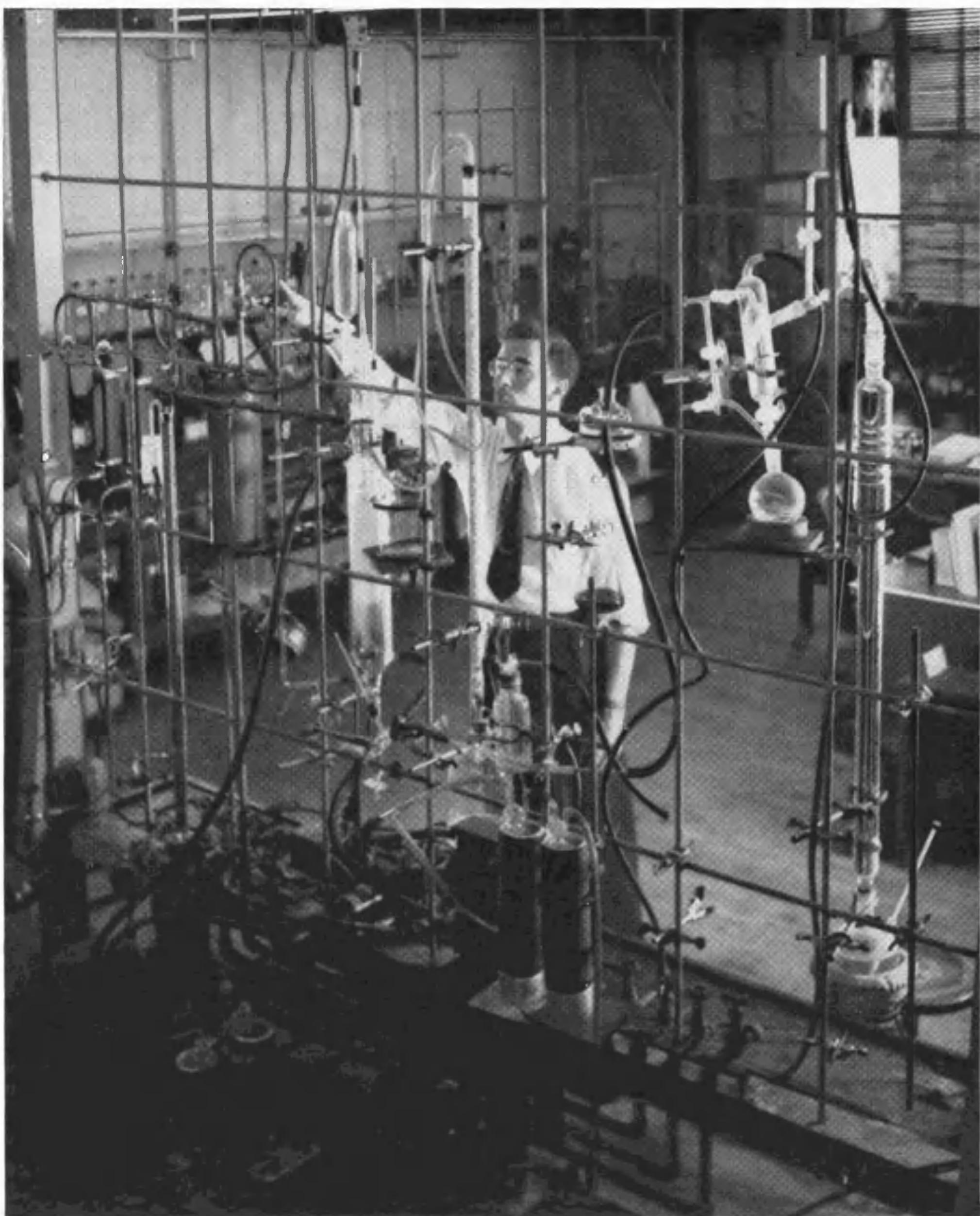
PACKAGING DATA. Guanidine compounds are not classified as dangerous by the Interstate Commerce Commission. They are suitably packed in fiber drums or multiwall paper bags with the exception of guanidine hydrochloride which is strongly deliquescent and must be packed in tightly closed drums. Guanidine hydrochloride should be kept closed and stored in a dry place.

TYPICAL ANALYSES. Table III shows typical analyses of the three guanidine salts presently available in commercial quantities.

TABLE III
Typical Analyses of Commercial Guanidine Salts

Property	Guanidine Carbonate	Guanidine Hydrochloride	Guanidine Nitrate
Assay	Not less than 96%	Not less than 95%	Not less than 98%
Ammeline-Ammelide	4.0%	—	—
Ammonia	0.13%	—	—
Ammonium Chloride	—	Not more than 1.7%	—
Ammonium Nitrate	—	—	Not more than 0.7%
Color	White	White	White
Insoluble Matter	Not more than 0.2%	Not more than 0.5%	Not more than 0.05%
Melamine	—	—	Not more than 0.5%
Moisture	Not more than 0.5%	Not more than 0.5%	Not more than 0.5%
Screen Size	Not <95% through 40 mesh	—	Not <99% through 12 mesh
Sulfates	Not more than 0.25% as SO_3	—	—
Ash	Not more than 0.2%	Not more than 0.2%	Not more than 0.05%

NITROGEN CHEMICALS DIGEST

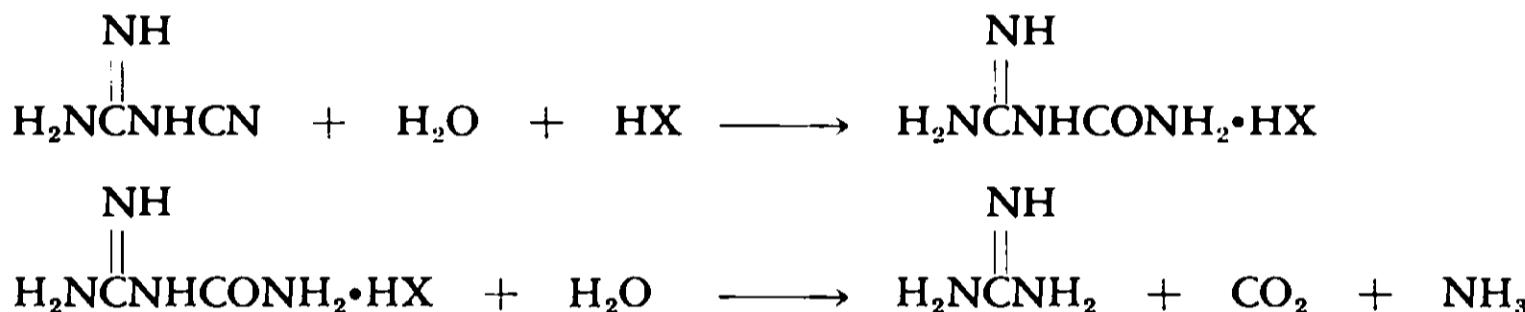


SYNTHESIS OF GUANIDINE

Guanidine may be synthesized by one of two general processes. The first and most convenient of these involves the addition of ammonia or ammonium salts to cyanamide or to dicyandiamide. The second method involves the replacement of the sulfur atom of thiourea (or the oxygen atom of urea) by ammonolysis. Guanylurea, biuret, and the like may also be used as starting materials for the latter process.

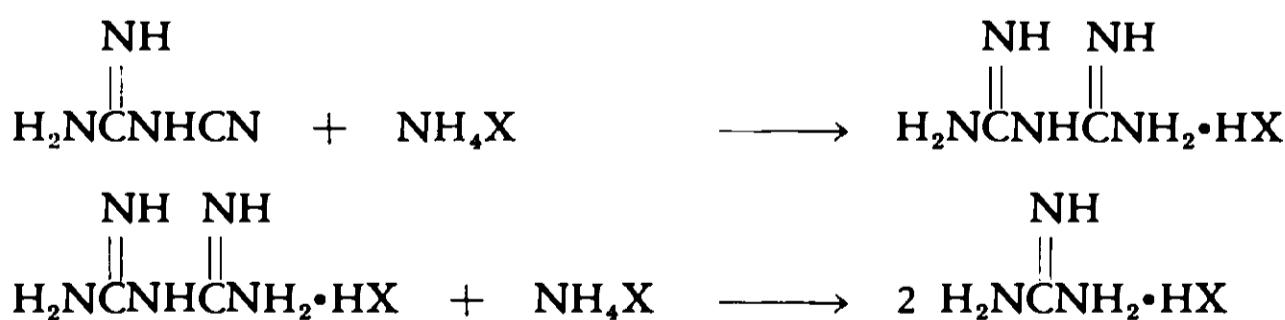
(1) FROM DICYANDIAMIDE

It has been known for some time that dicyandiamide may be converted in acid solutions to guanylurea and thence to a guanidine salt.



A great many modifications, using either dicyandiamide or guanylurea as starting material, have been suggested for this reaction (37, 101, 152, 164, 264, 295, 427, 461). The hydrolysis has also been conducted in ammoniacal solution (102).

The yield of guanidine salt may be increased from one to two moles per mole of dicyandiamide if ammoniation rather than hydration is used. This reaction is preferably conducted by fusing dicyandiamide with an ammonium salt at about 170°C. (284, 333, 403, 413). If wet fusion is used, lower yields are obtained. The mechanism of the reaction is said to involve ammoniation to the biguanide salt which is unstable at these temperatures and is split by another molecule of ammonium salt to yield the guanidine salt (333).



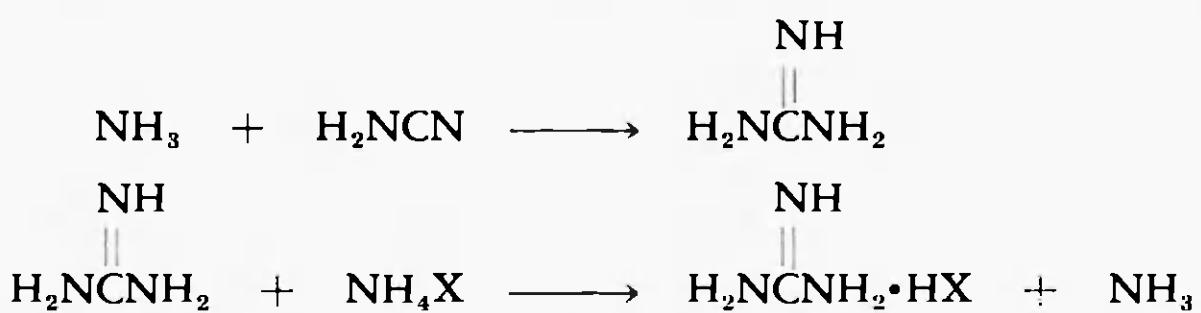
A recent technique in which the reaction is run in liquid ammonia has the advantage of giving better yields and is a less hazardous process to operate (333).

(2) FROM CYANAMIDE

One of the first syntheses of guanidine consisted of an ammoniation of aqueous cyanamide with an ammonium salt (132).



The mechanism of this reaction apparently requires the presence of free ammonia (9, 332, 333). The function of the ammonium salt is to stabilize the guanidine formed, for guanidine is a much stronger base than ammonia and therefore displaces ammonia from its salt.

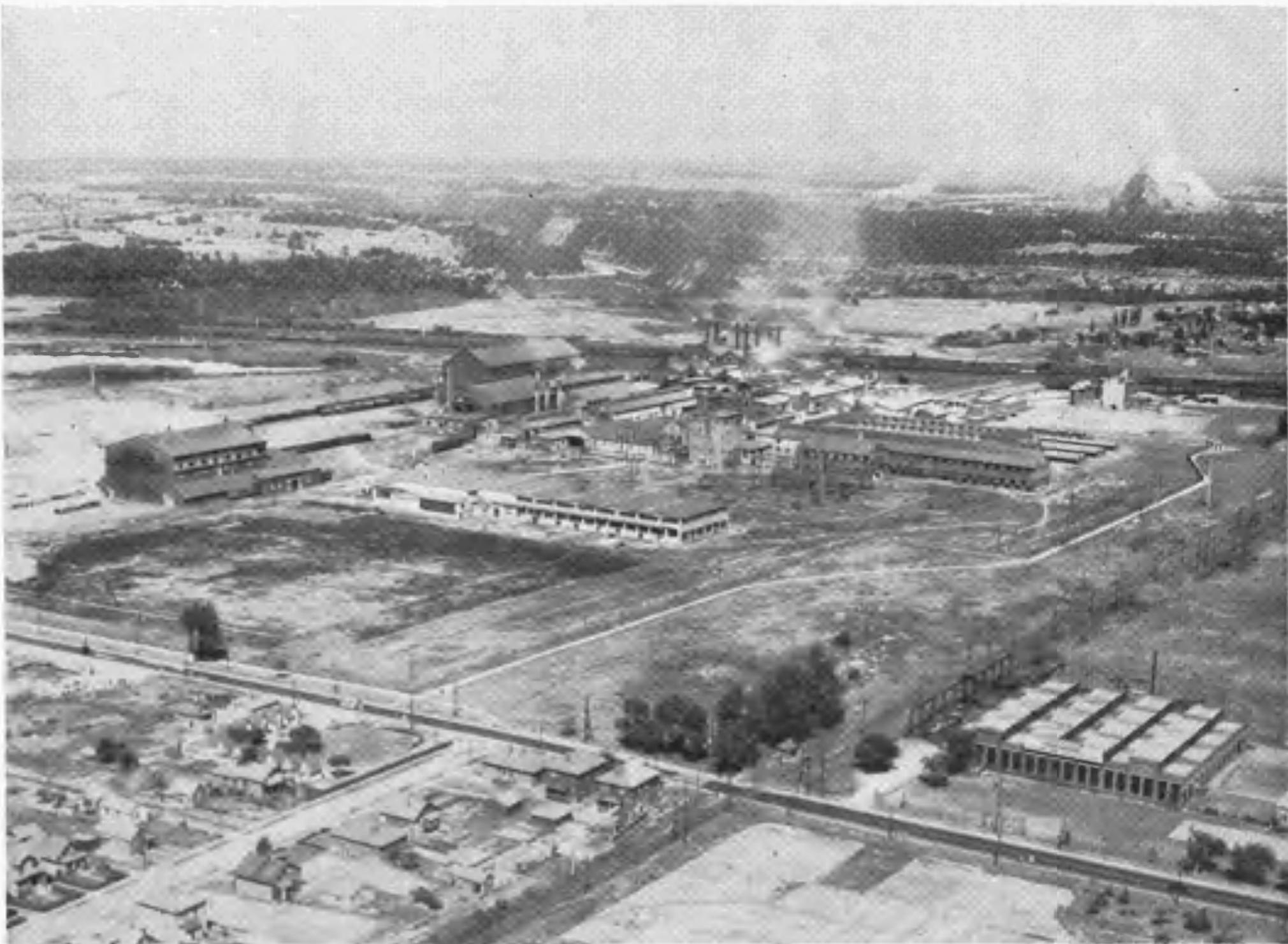


In the absence of free ammonia reaction will occur only at elevated temperatures (150-170°C.), at which temperatures sufficient ammonia is probably produced by decomposition of cyanamide to initiate the reaction. Better yields are obtained if the dry reactants, cyanamide and an ammonium salt, are fused together (333), although the method using aqueous cyanamide is a more practical process.

Calcium cyanamide, AERO* Cyanamid, may be added to molten ammonium salts to form guanidine salts (333) but this method is not advisable for guanidine nitrate preparation because the carbonaceous impurities present in AERO Cyanamid present an explosion hazard when this material is fused with ammonium nitrate (333). The addition of urea to the calcium cyanamide-ammonium salt mixture has been successfully employed to produce lower fusion temperatures (193, 489).

(3) MISCELLANEOUS METHODS

Guanidine may also be prepared by the ammonolysis of ammonium thiocyanate (199, 251, 255, 401), of urea (45, 279), and certain of its derivatives (46, 365, 439), of cyanogen iodide (24) and of orthocarbonates (204).



NIAGARA FALLS PLANT

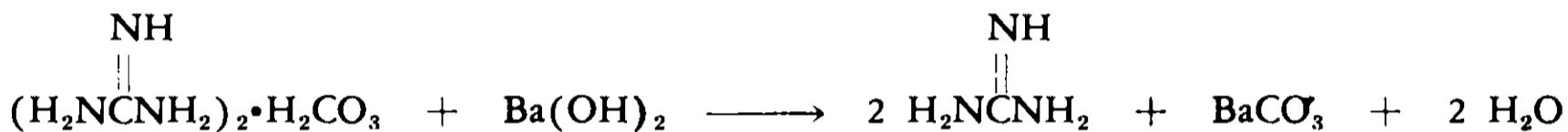
* Trade-mark

CHEMICAL PROPERTIES

The reactions of guanidine are those which one might anticipate for a strongly basic amino compound. It may be alkylated or acylated and it may be condensed with aldehydes and esters in the manner of other primary amines. The fact that the molecule contains two amino groups makes it suitable for the production of imidazoles, triazines and pyrimidines. A few of the reactions of guanidine, for example hydrolysis, are more characteristic of compounds containing the imino grouping. These and other chemical properties are summarized in the Reaction Chart (center spread) and are discussed in some detail below.

ISOLATION OF FREE GUANIDINE BASE

Guanidine may be freed from its salts by treatment with a reagent which will precipitate the salt anion.

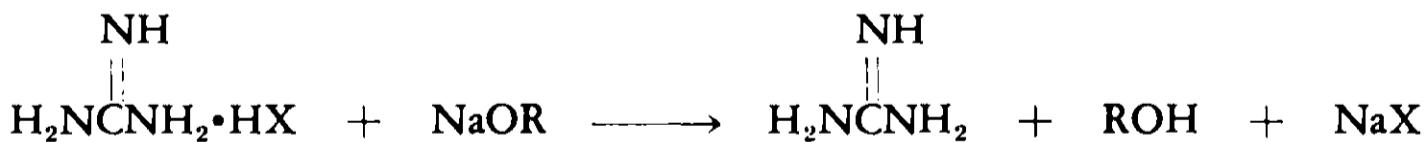


To obtain very pure guanidine, guanidine carbonate is treated with somewhat less than the theoretical amount of barium or calcium hydroxide in aqueous solution (311). After filtering the precipitated barium carbonate the filtrate may be concentrated and diluted with ethanol. Thereupon the excess guanidine carbonate is precipitated and the dissolved guanidine remains in a pure state.

A typical procedure used in our laboratory is as follows: Mix 100 g. of guanidine carbonate with 400 cc. of water. While stirring, slowly add a slurry of 43 g. of calcium hydroxide in 50 cc. of water. Agitate for 15 minutes and filter. Wash the filter cake with small portions of water until the original filtrate and washings aggregate about 550 cc. This solution will contain approximately 10% free guanidine. The temperature of the filtrate should be maintained below 25°C. to avoid decomposition. See Fig. 8, page 15.

On the other hand, the carbonate may be first converted into sulfate by treatment with sulfuric acid. The sulfate ion may then be removed quantitatively either with barium hydroxide (362) or by treatment with potassium hydroxide or amide in liquid ammonia (196, 443).

The use of solvents other than water is often desirable. Both potassium hydroxide (233, 287) and sodium alkoxides (298, 329, 455) have been used in alcoholic solutions with a number of guanidine salts.

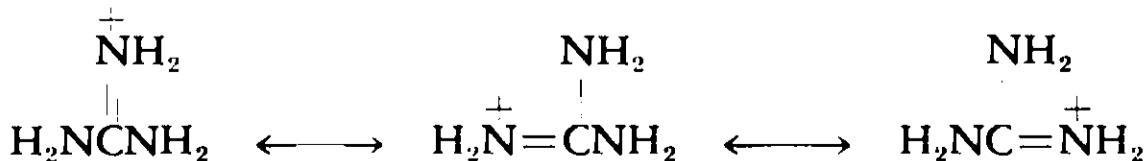


STRUCTURE OF GUANIDINE SALTS

We shall write the structural formula of a guanidine salt as $\text{H}_2\text{NCNH}_2 \cdot \text{HX}$ throughout this booklet,

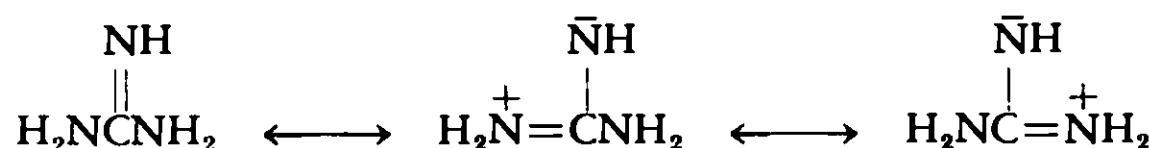
although the actual salt structure is probably $\left[\begin{array}{c} \text{NH}_2 \\ || \\ \text{H}_2\text{NCNH}_2 \end{array} \right]^+ \text{X}^-$ (281). Evidence for this structure derives

from the fact that it may account for the strongly basic nature of unsubstituted guanidine. Pauling (338) has suggested that this basicity is due to the ability of the guanidinium ion to resonate among three structures which are all equivalent,



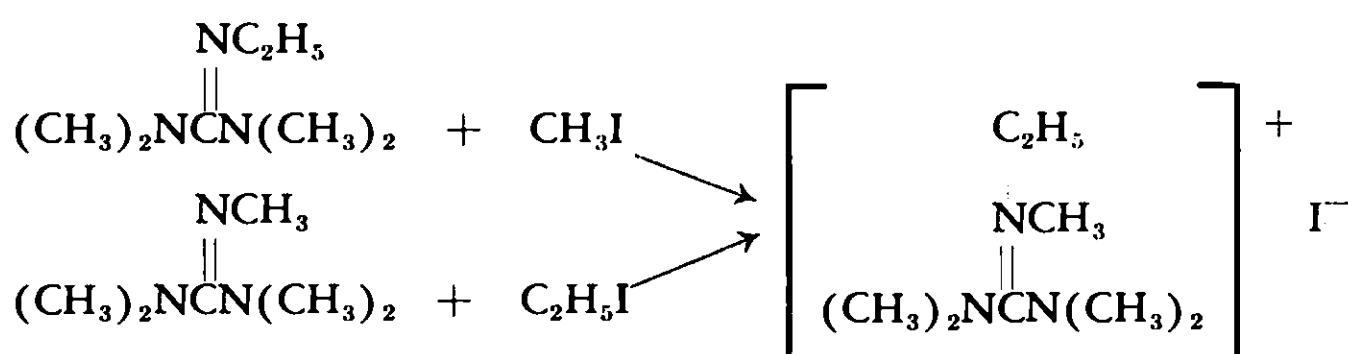
whereas guanidine itself resonates among three structures which are not equivalent.

NITROGEN CHEMICALS DIGEST

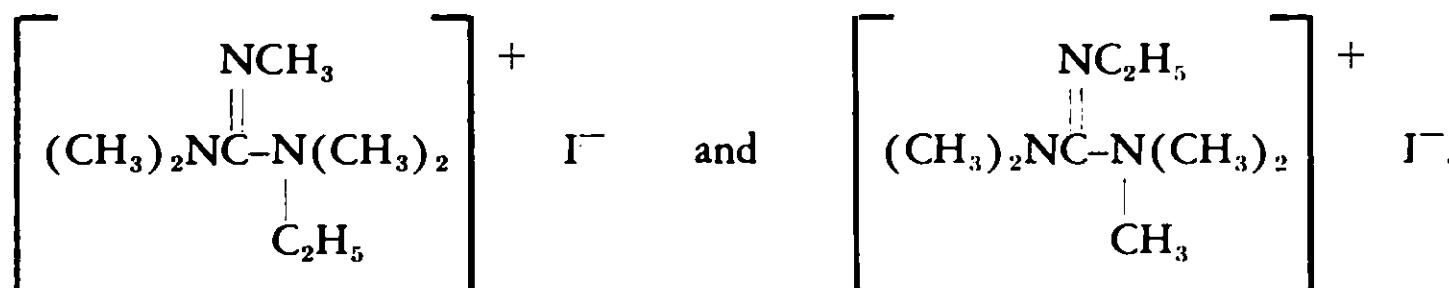


The increase in resonance energy which takes place upon ionization is sufficient to account for the basic strength of guanidine. Quantum mechanical evidence for the existence of resonance in the guanidinium structure has been obtained by Kellner (244).

Lecher and Graf (260) have shown that in pentasubstituted guanidines the imino nitrogen is indeed the seat of basicity; for the methiodide of N,N,N',N'-tetramethyl-N''-ethylguanidine was found to be identical with the ethiodide of pentamethylguanidine.



If the basicity were seated at one of the amino nitrogens, the two reactions would have yielded different products,

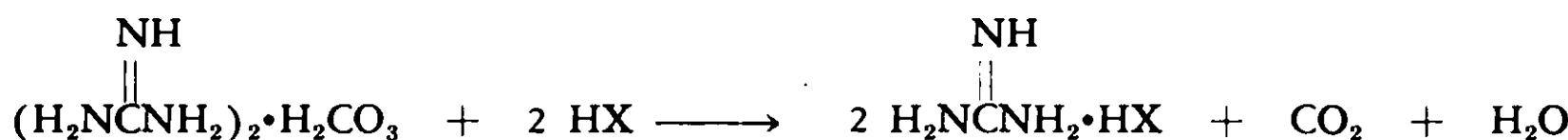


SALT FORMATION

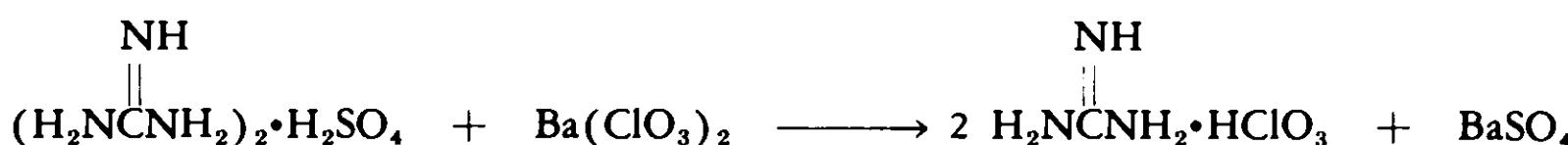
Guanidine is sold in the form of one of its salts, generally the carbonate, nitrate or hydrochloride. Any number of other salts may be prepared from these common sources. This can be done in two ways:

(1) BY DOUBLE DECOMPOSITION

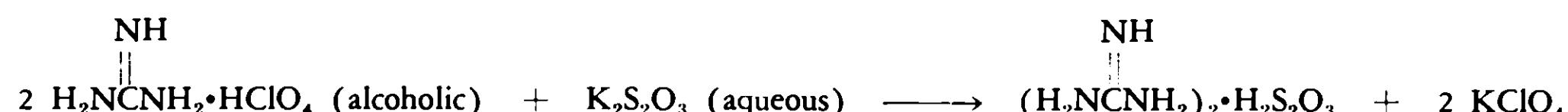
A guanidine salt may be treated with the new acid:



where X is the anion of the desired salt. Guanidine carbonate is most often used for this method because of the volatility of the freed carbon dioxide. The thiocyanate has also been used in sulfuric acid to produce guanidine sulfate, the HCNS being distilled out (167). Double decompositions leading to precipitation of the undesirable anion have been found effective (287):

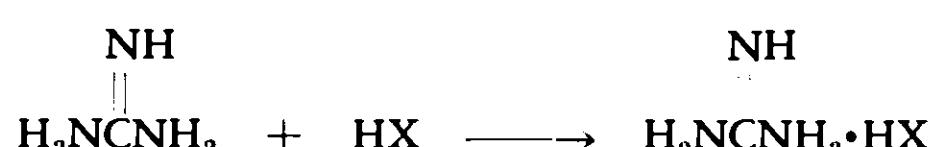


The use of organic solvents may be helpful in producing precipitation (287):



(2) FROM FREE GUANIDINE

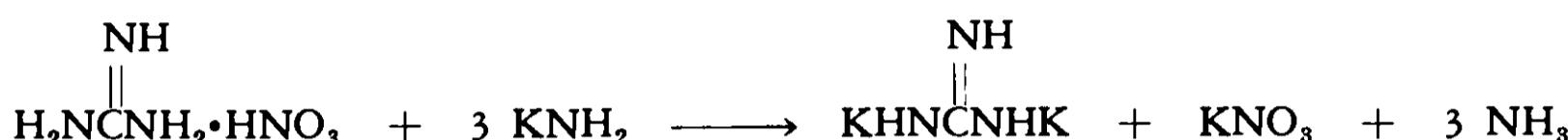
If free guanidine is first liberated from its salt it may then be treated with any desired acid.



NITROGEN CHEMICALS DIGEST

The salt formation may be conducted in aqueous or alcoholic solution or by adding the solid base to a liquid acid (287) if this is convenient.

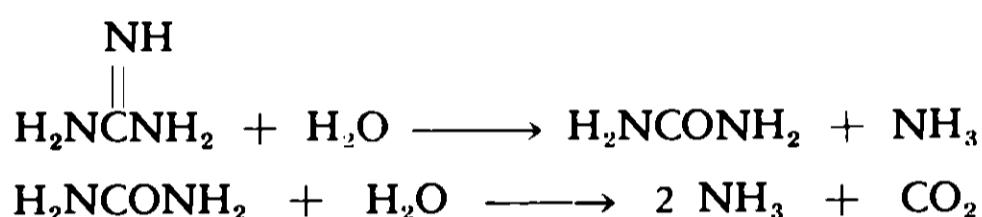
Metal salts of guanidine are readily formed in the reaction between guanidine nitrate and a metal amide in liquid ammonia.



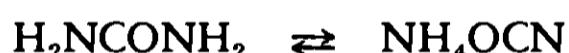
The silver and alkali metal salts have been prepared in this manner (153).

REACTION WITH WATER

In 1866 Hofmann demonstrated that guanidine may be hydrolyzed to carbon dioxide and ammonia by boiling with water (204). Early workers assumed that guanidine was first hydrolyzed to urea, which then reacted with water to yield the two gaseous products.



Evidence for this was obtained by the isolation of urea from guanidine hydrolysis with barium hydroxide. More recent work (39, 259) has shown that guanidine is slowly hydrolyzed to urea by the action of water at room temperature and that this hydrolysis is catalyzed by alkali. If aqueous guanidine solutions are boiled, small amounts of ammonium cyanate are also obtained, apparently by rearrangement of the urea produced.



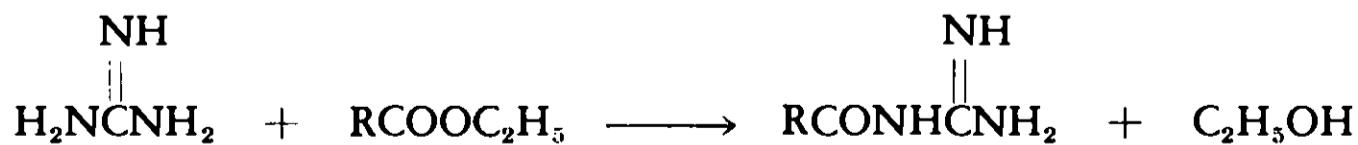
The rate of decomposition of guanidine in aqueous solution is indicated (9) in Figure 8.

Guanidine salts of strong acids are completely stable to boiling water. Guanidine carbonate is slowly hydrolyzed, very likely because of dissociation to free guanidine (40).

REACTION WITH ACYLATING AGENTS

(1) ESTERS

Monoacyl guanidines are readily prepared by treating the free base with esters (324, 406, 454). The reaction is usually effected in alcoholic solution, either with or without a condensing agent such as sodium ethoxide.



This reaction proceeds smoothly and sometimes exothermically at room temperature. The esters of dibasic acids, except those of oxalic and malonic acids, give linear acyl guanidines (298). The oxalates and malonates yield cyclic compounds as will be seen below.

(2) ACYL HALIDES

Acid chlorides (253, 318) and bromides (12) react readily with guanidine or its salts to produce acyl guanidines.

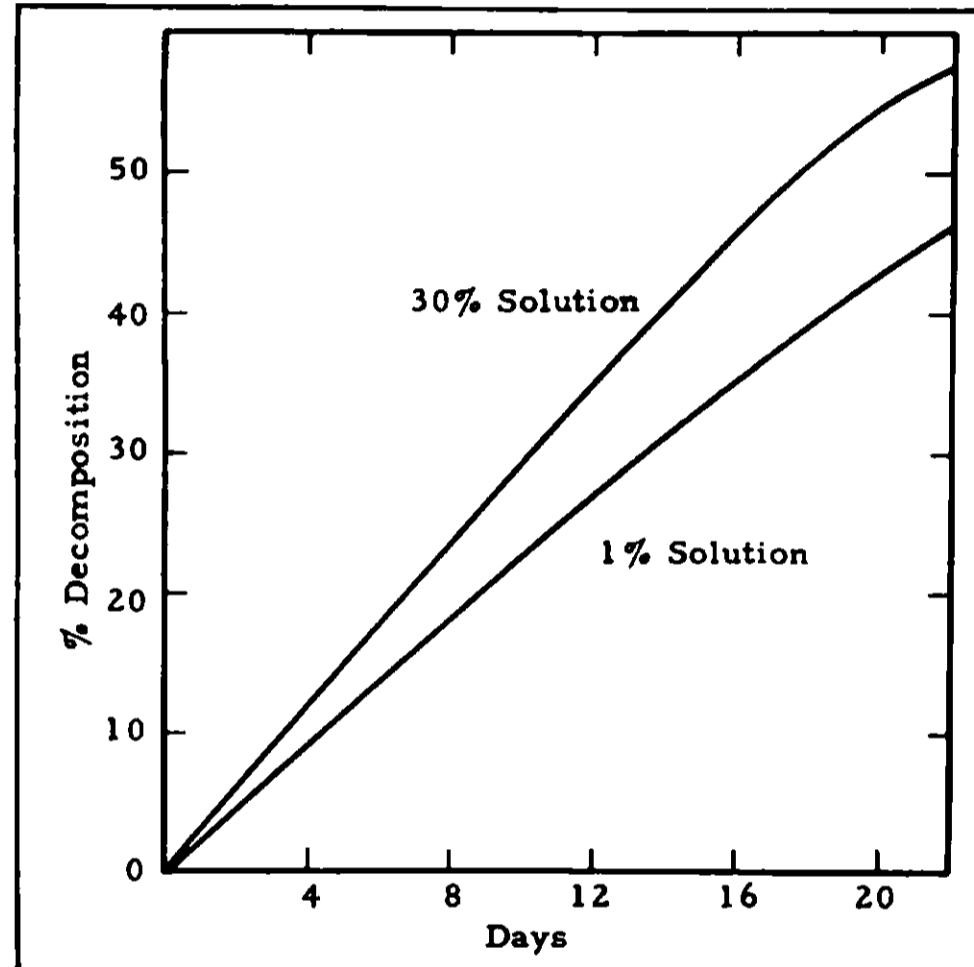
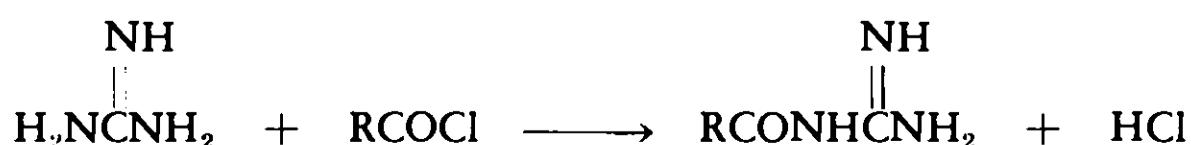
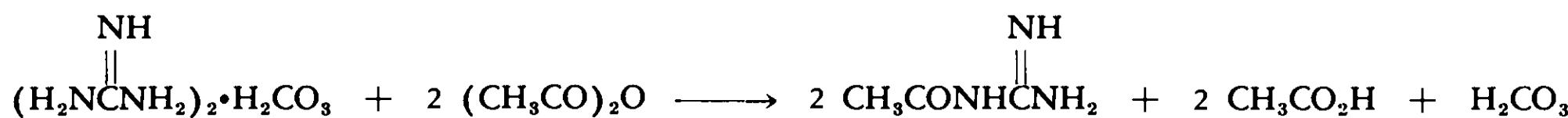


Figure 8—Decomposition of Free Guanidine Base in Aqueous Solution at 29°C.

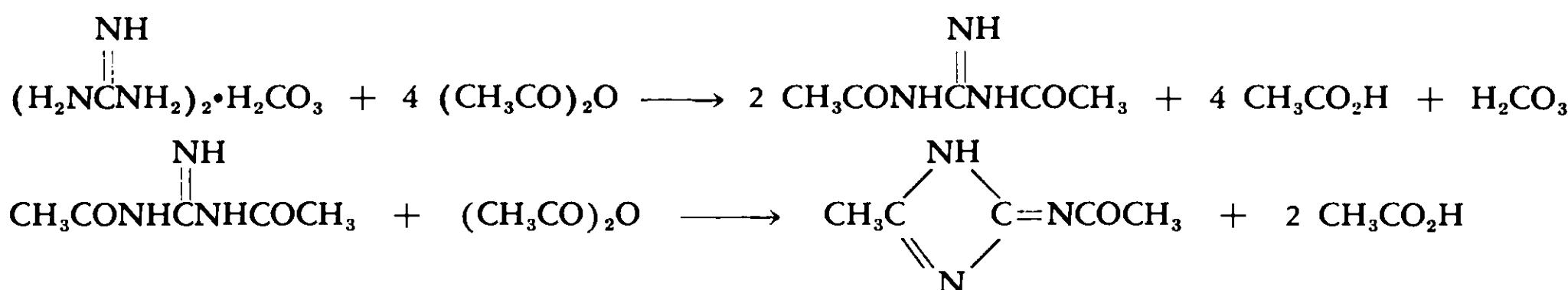
NITROGEN CHEMICALS DIGEST

(3) ACID ANHYDRIDES

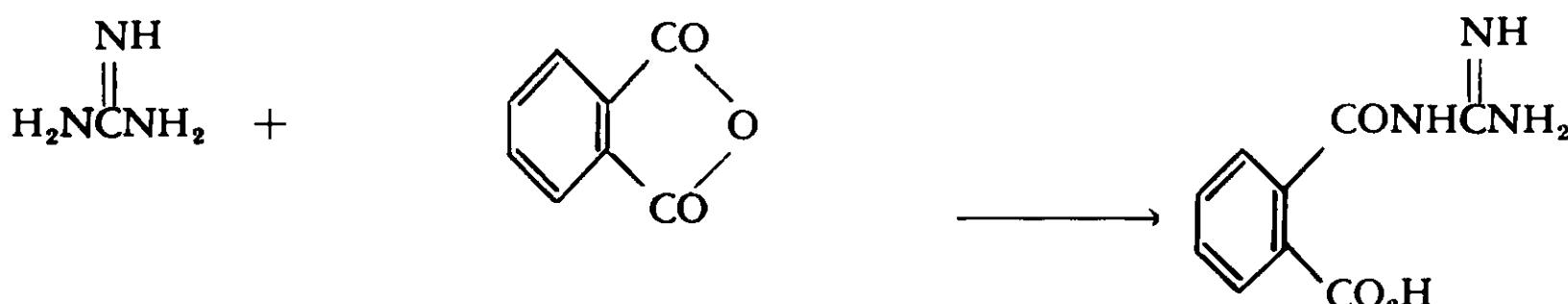
When guanidine or one of its salts is treated with only a slight excess of an acid anhydride the mono-acyl derivative may be isolated (253).



In the presence of two moles of anhydride the diacyl derivative is obtained; and if larger excesses are used this product is dehydrated (253).



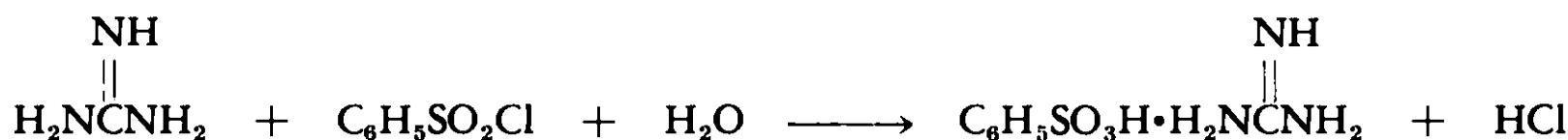
With phthalic anhydride, the guanidino acid is obtained (297).



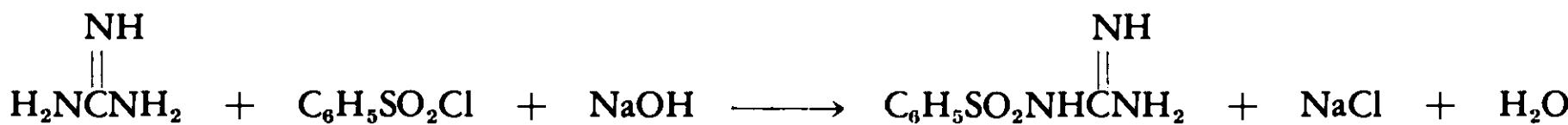
REACTION WITH SULFONATING AGENTS

(1) SULFONYL HALIDES

Depending upon the conditions used, the reaction between arylsulfonyl halides and guanidine salts will yield either the sulfonyl guanidine or the guanidine sulfonate. The latter is obtained (243, 345) if insufficient alkali is present to neutralize the HCl which is produced in the reaction.

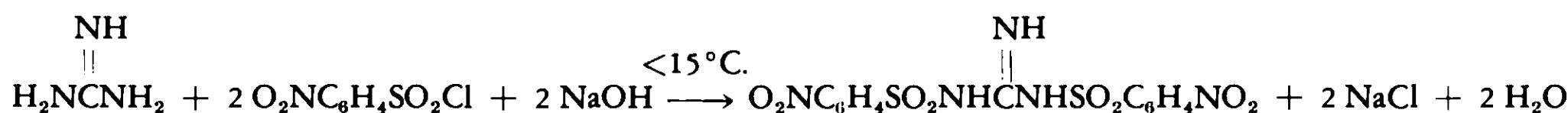


The yield of the sulfonyl guanidine increases in proportion to the concentration of alkali (345).



This reaction has also been effected in pyridine solution (114) although the yields are somewhat lower (345).

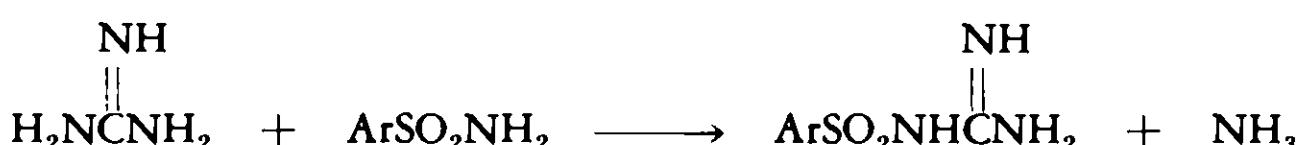
Particular interest has centered on the reaction of sulfonyl chlorides with guanidine or its salts, because of the therapeutic value of "sulfaguanidine" and its derivatives (288). In most cases either the acetyl derivative of sulfanilyl chloride (114, 170, 247b, 274, 288, 322, 485) or p-nitrobenzene sulfonyl chloride (354, 376, 485) have been used since these are readily converted by hydrolysis or reduction into sulfaguanidine. Sulfonyl fluorides (469) or bromides (10) may also be used. Various substituted sulfonyl chlorides give similar results (74, 130, 140, 196, 245); and by properly varying the conditions the reaction may be made to produce disulfonyl derivatives (20, 348).



(2) SULFONAMIDES

Although carboxylic acid amides do not react with guanidine or its salts (158), sulfonamides do.

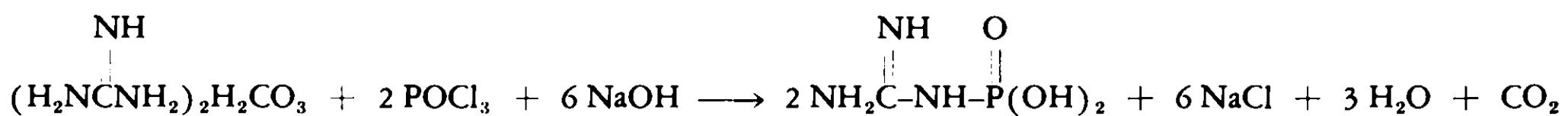
NITROGEN CHEMICALS DIGEST



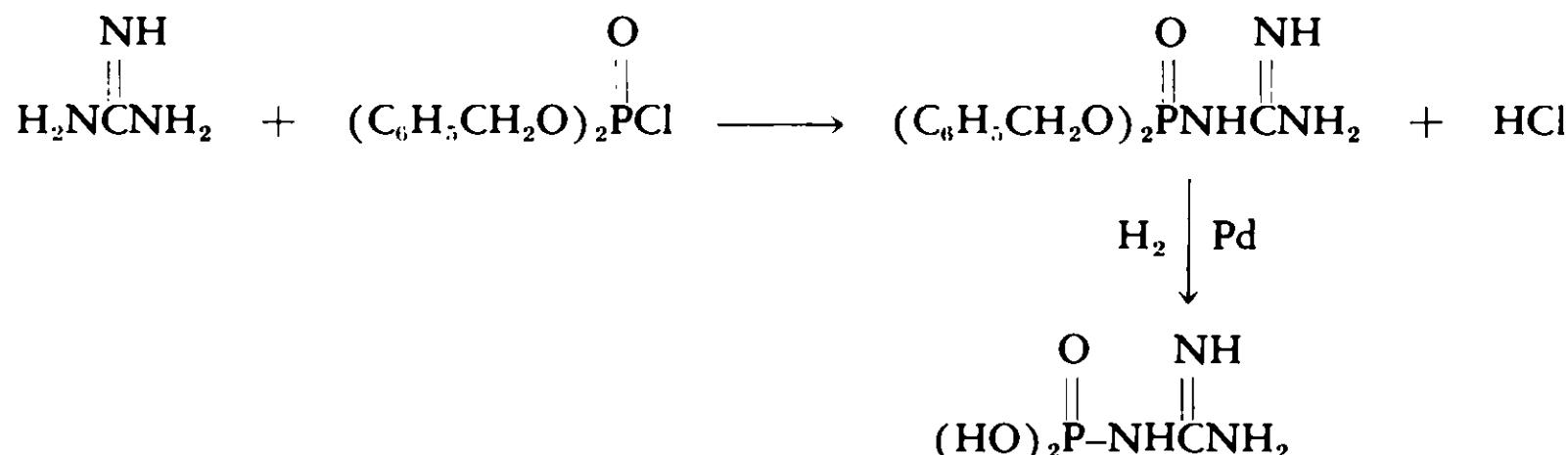
The reaction is usually effected by heating the reactants at about 170°C. (43, 44, 81, 111, 142, 166, 226, 307) either in the dry state or in aqueous solution. Sulfaguanidine may also be prepared by the fusion of sulfanilamide and dicyanidamide (112).

REACTION WITH PHOSPHORYLATING AGENTS

Three phosphorylating agents have been used with guanidine. Phosphorus oxychloride reacts with guanidine carbonate in the presence of alkali to produce guanidinophosphoric acid (144).



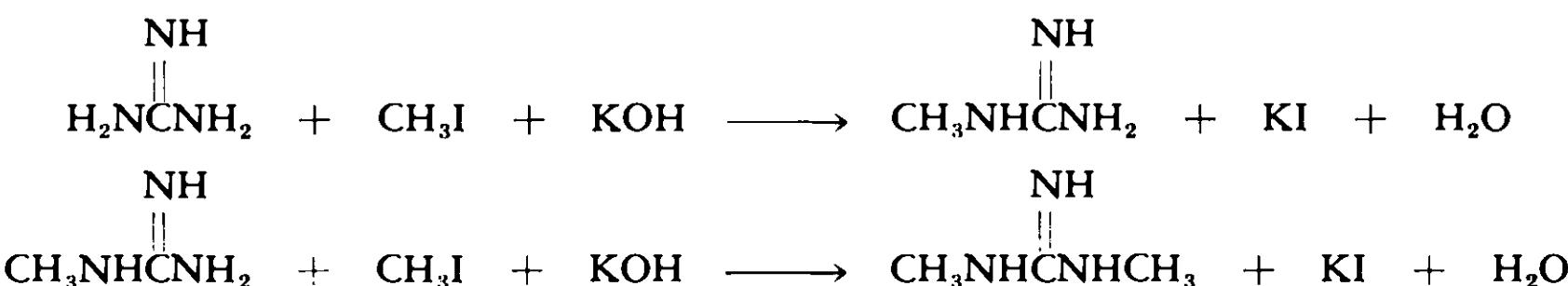
This very strong dibasic acid has also been prepared by reaction of free guanidine with diphenyl (161) or dibenzyl (110) phosphoryl chloride, followed by hydrogenation.



REACTION WITH ALKYLATING AGENTS

(1) ALKYL HALIDES

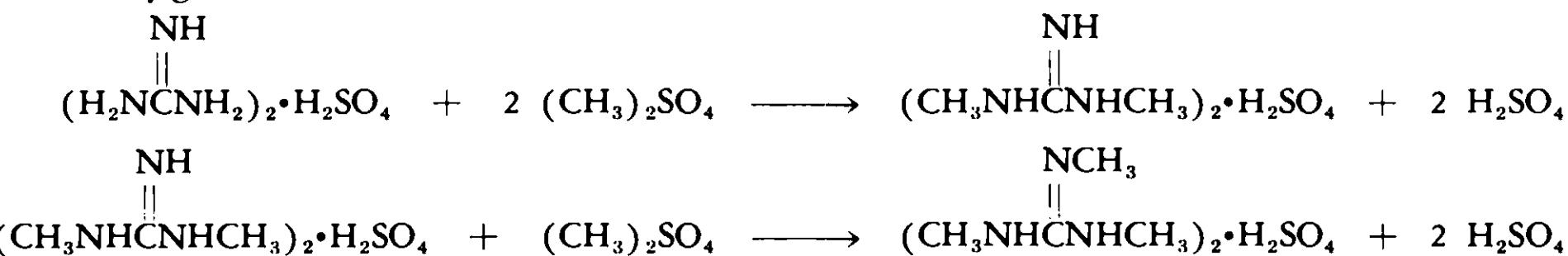
Guanidine reacts with methyl iodide only in the presence of caustic alkali forming both methyl- and dimethylguanidine (390).



The silver salt of guanidine undergoes double decomposition with methyl iodide, the mixture of methylated products being unidentified (390). Alkylene dihalides (168) and certain chloropyrimidines (246) will alkylate guanidine in a similar fashion.

(2) DIMETHYL SULFATE

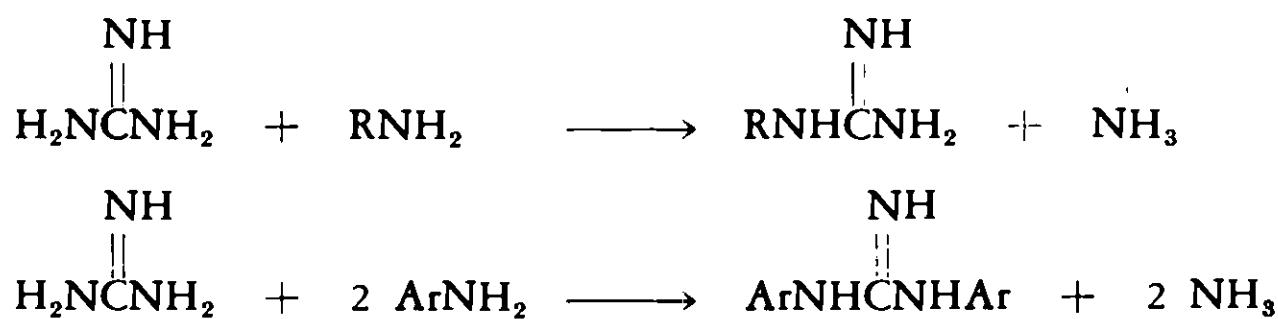
Dimethyl sulfate reacts with guanidine sulfate at 150-160° in a sealed tube (390) to produce symmetrical di- and tri-methylguanidines.



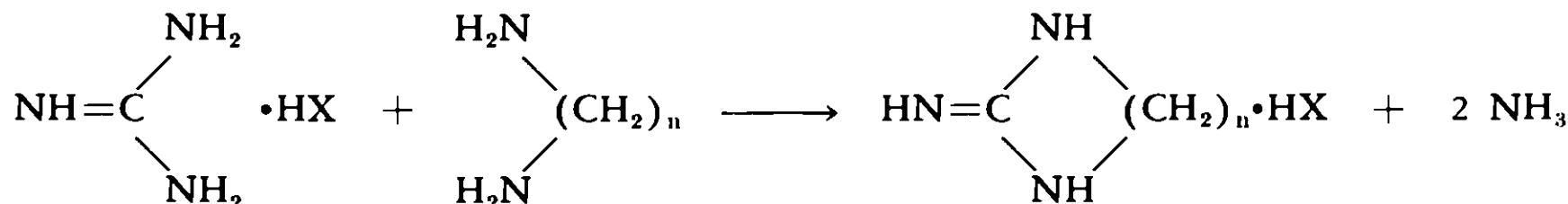
(3) AMINES

Primary aliphatic and aromatic amines condense with guanidine or its salts with the loss of ammonia. The aliphatic amines result in mono-substitution (169, 356, 386, 448) whereas the aromatic products are predominately disubstituted (205).

NITROGEN CHEMICALS DIGEST

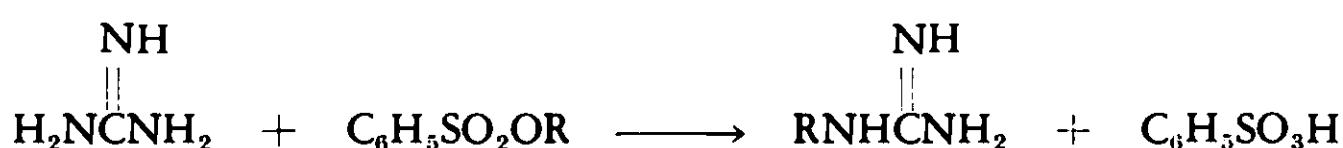


If guanidine salts are heated with polymethylene diamines of two to five carbon atoms, ammonia is evolved and the corresponding salts of aminodiazocycloalkanes are formed (49).



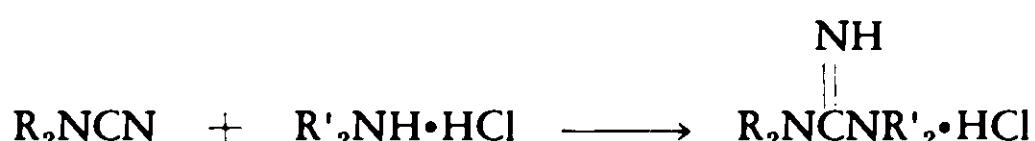
(4) WITH ALKYL BENZENESULFONATES

Guanidine may be alkylated by alkyl esters of arylsulfonic acids (219, 361).

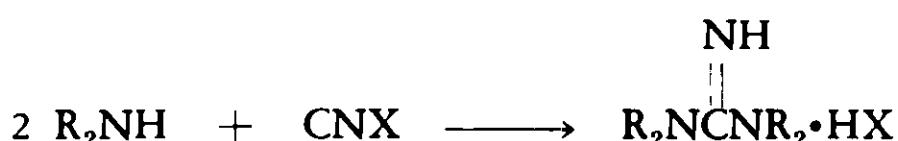


Although guanidine is indeed alkylated by these various reagents, it must be pointed out that it is generally more convenient to prepare alkyl guanidines by one of five other methods:

(a) The reaction of cyanamides with amine salts (Erlenmeyer's Synthesis) (132).



(b) The reaction of a cyanogen halide with amines (Hofmann's Cyanogen Halide Method) (203).



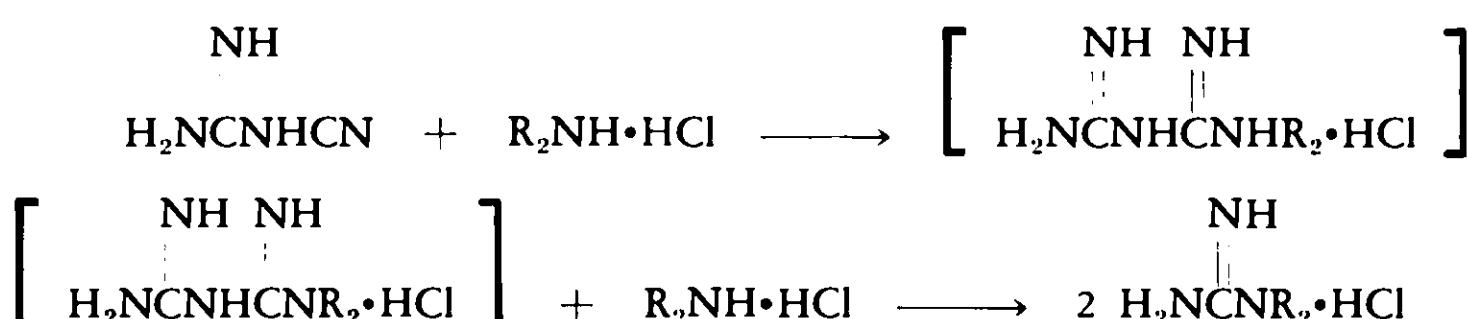
(c) The reaction of a halide or sulfate salt of an S-methyl- (or ethyl-) isothiourea with an amine (Rathke's Synthesis) (365).



(d) The reaction of thioureas with amines and a desulfurizing agent (Hofmann's Desulfurization Method) (206).



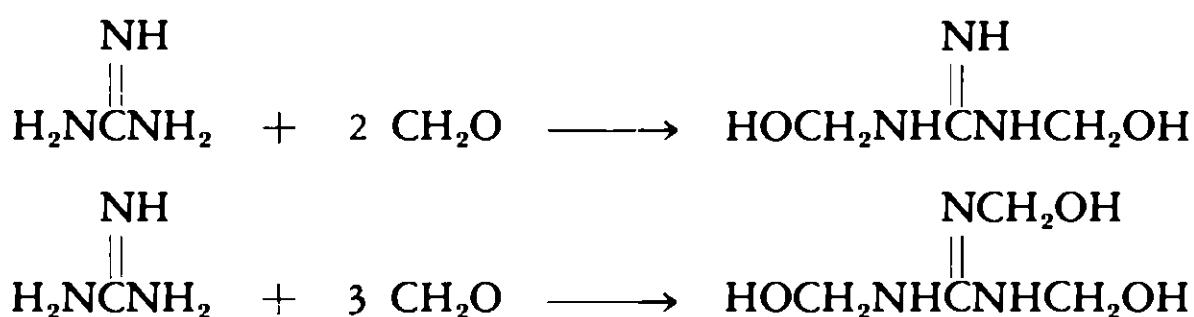
(e) The fusion of amine salts with dicyandiamide (473).



NITROGEN CHEMICALS DIGEST

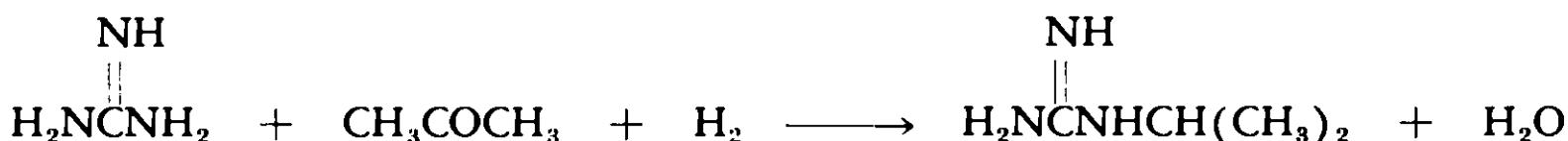
REACTION WITH ALDEHYDES AND KETONES

A very important chemical property of guanidine is its ability to react with aldehydes, especially formaldehyde, with the production of useful resinous materials which will be discussed in a later section. The reaction apparently involves the formation of di- or tri-methylol guanidines which immediately polymerize with loss of water or react with other guanidine molecules with loss of ammonia, and so forth (13).



The properties of the resinous or syrupy products depend on the nature of the guanidine and aldehyde used, the relative proportions of the two reactants, the time of heating and the condensing agent, if any (13).

In the presence of hydrogen and a hydrogenation catalyst at super-atmospheric pressure the reaction of guanidine with aldehydes and ketones results in alkylation (187).

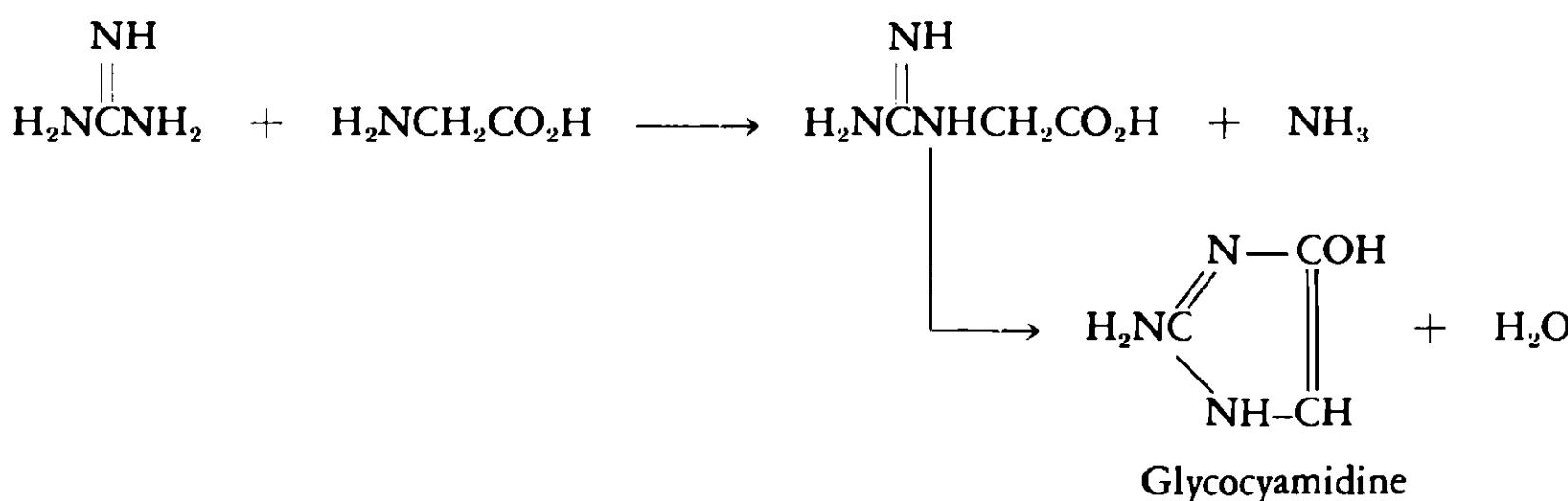


By this procedure it is possible to replace one or more of the hydrogen atoms of guanidine depending upon the amount of aldehyde or ketone used.

FORMATION OF HETEROCYCLIC COMPOUNDS

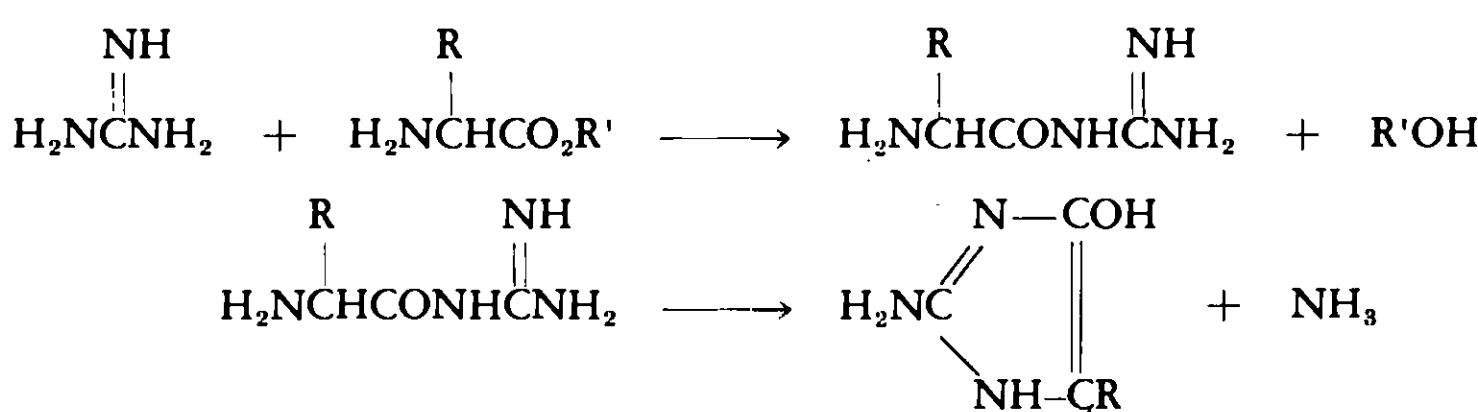
(1) AZOLES

Esters, acids, and the like, which are substituted in the alpha-position with a suitable functional group will form cyclic compounds on condensation with guanidine. An example of this is the formation of "glycocyamidine" from glycine (254). The first product of the reaction between glycine and guanidine is guanidinoacetic acid. This is converted into glycocyamidine by heat with loss of water.



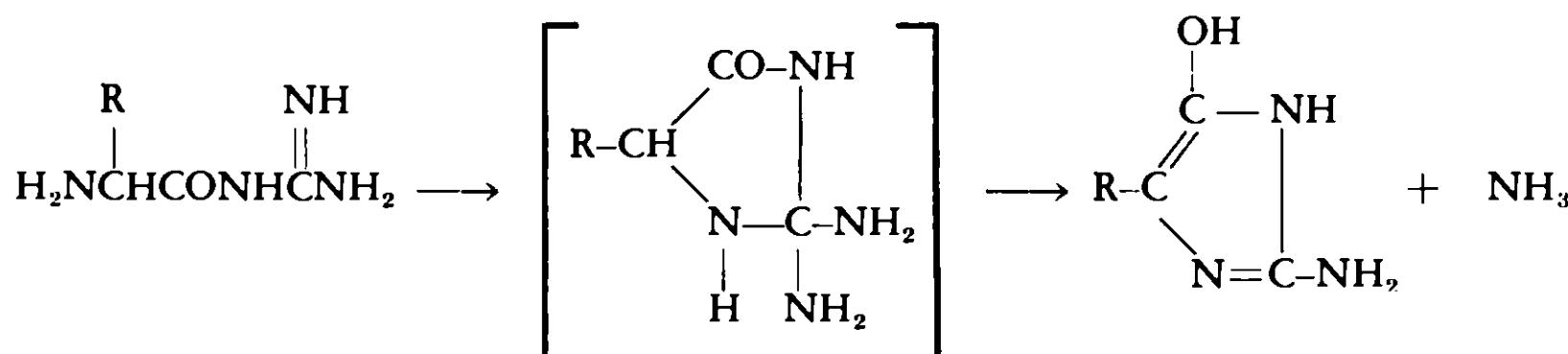
Similar reactions have been effected with other amino acids (128).

Alpha-amino esters react with guanidine with preliminary acylation. The "glycocyamidine" type of product then results by deammoniation (1, 454).

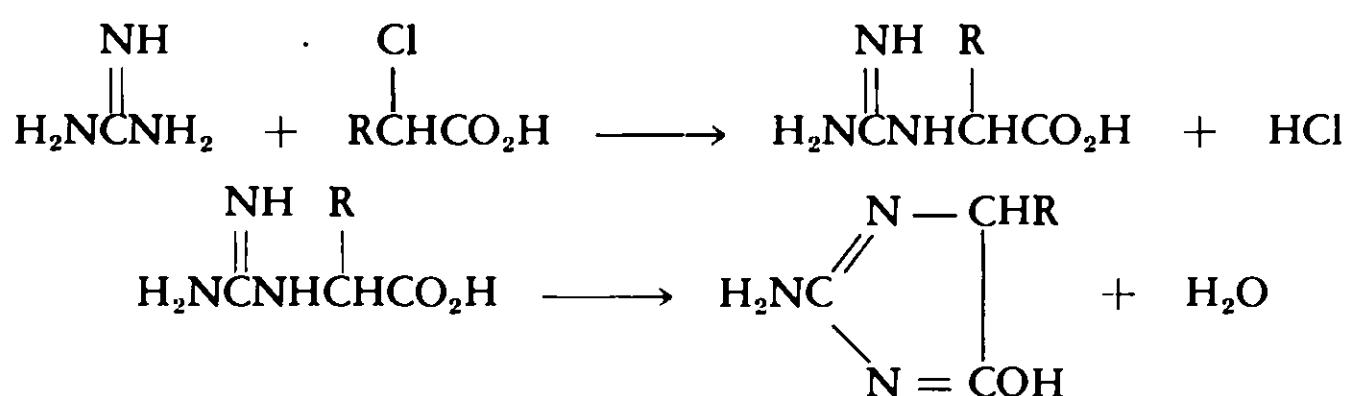


NITROGEN CHEMICALS DIGEST

Aberhalden and Sickel (1) demonstrated that the nitrogen atom is split off from the guanidine nucleus and suggest the following mechanism for the cyclization step.



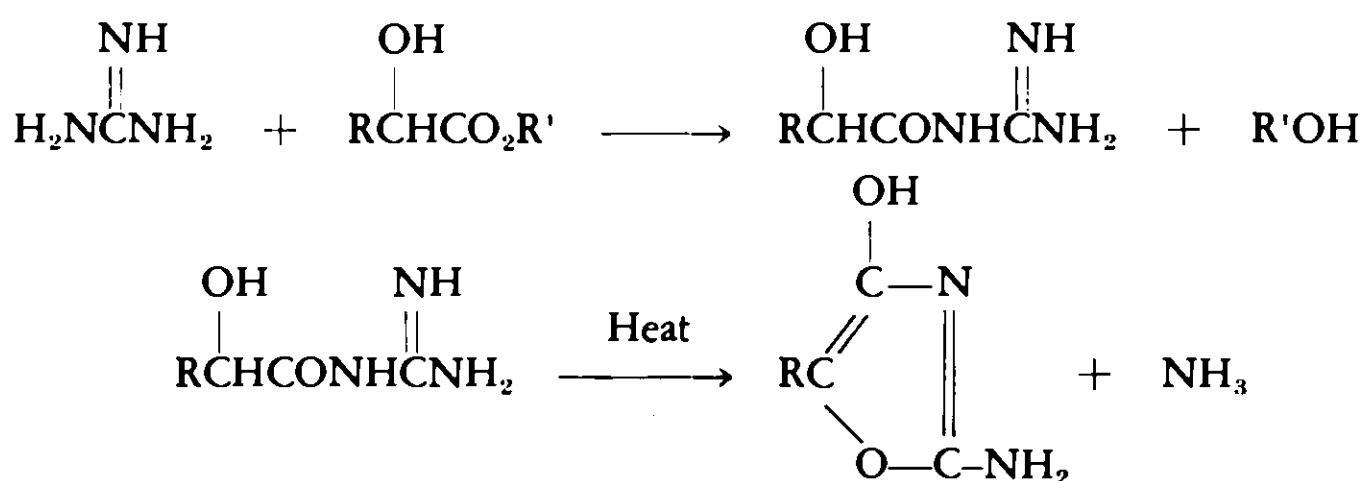
Acids and esters containing alpha-halogen atoms also form cyclic products with guanidine. In the case of alpha-halo acids, the reaction first yields guanidino acids which may (362) or may not (128) be isolated before dehydration occurs.



With halogenated esters acylation first occurs, and the reaction is readily stopped at this point (453).



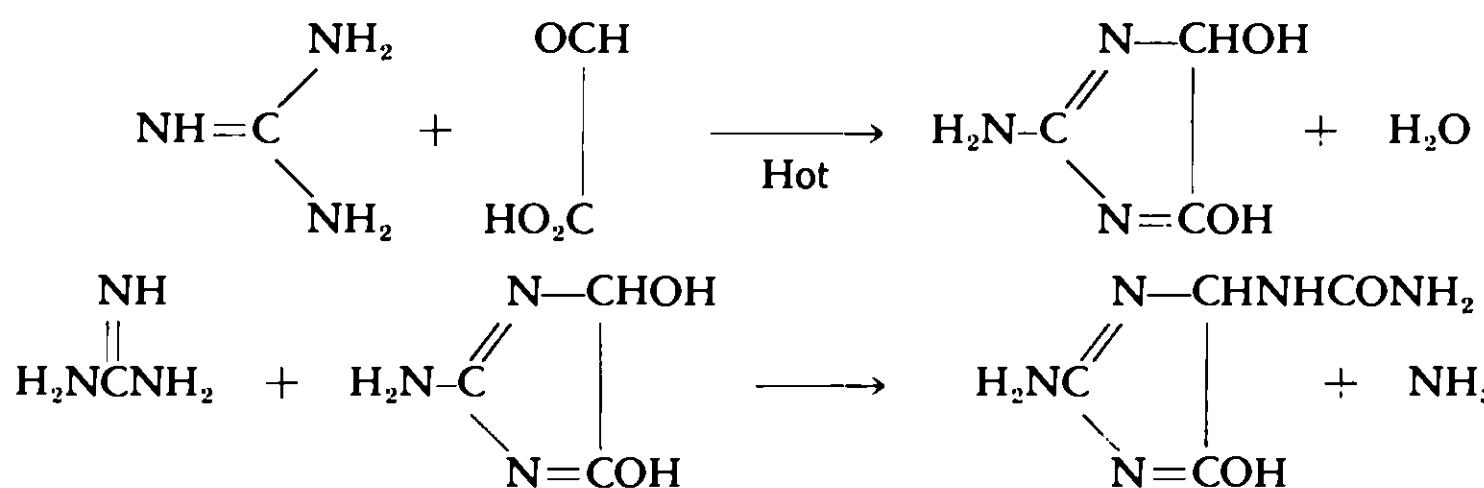
Alpha-hydroxy esters also immediately acylate guanidine, but the resulting compounds are readily deammonated to oxazoles (454).



Glyoxylic acid reacts with guanidine carbonate in the cold in the manner of a simple aldehyde.

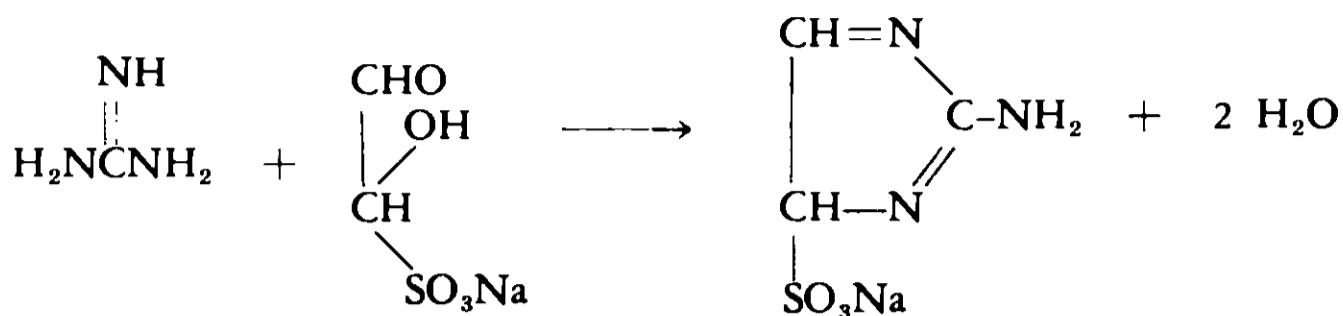


If the reaction mixture is heated, however, cyclization occurs together with an interesting secondary reaction to form imino-allantoin (240).

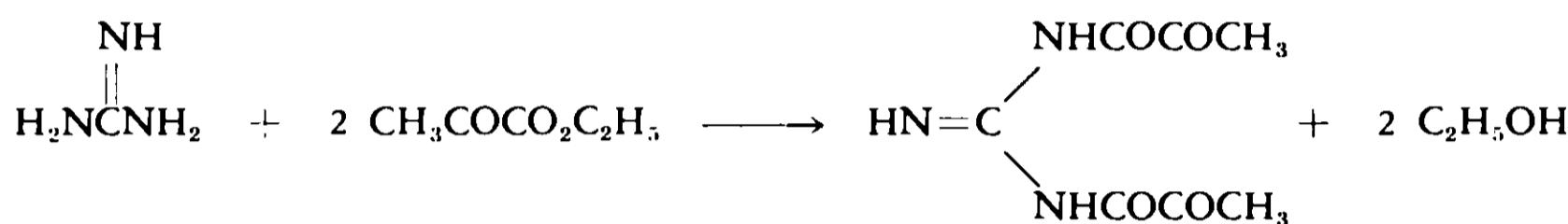


NITROGEN CHEMICALS DIGEST

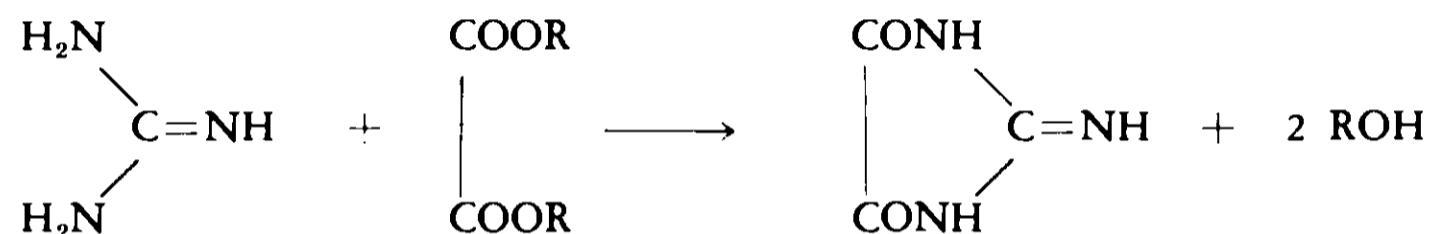
The bisulfite addition compound of glyoxal also undergoes an interesting cyclization reaction with guanidine (126).



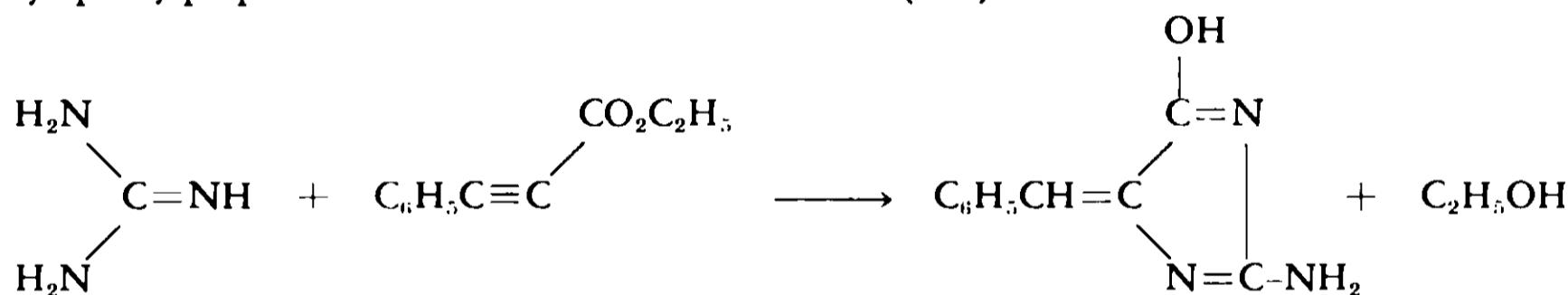
Ethyl pyruvate, which might be expected to react in a similar manner, apparently does not go beyond the acylation stage (159).



Oxalic ester readily reacts with guanidine in the presence of sodium alcoholate to yield oxallyl guanidine (298, 450).



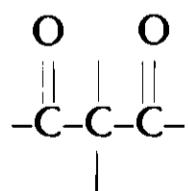
Ethyl phenylpropionate condenses in a similar manner (382).



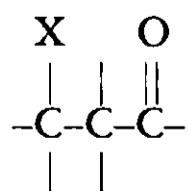
(2) PYRIMIDINE FORMATION

Because of the ease with which the therapeutically valuable 2-aminopyrimidines are synthesized from guanidine or its salts, a great deal of work has been done on this subject. The compounds which condense with guanidine to form pyrimidines may be divided into three structural groups:

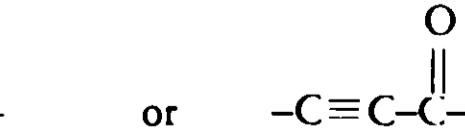
(a) The beta, beta-dicarbonyl structure,



(b) The beta-substituted carbonyl structure,



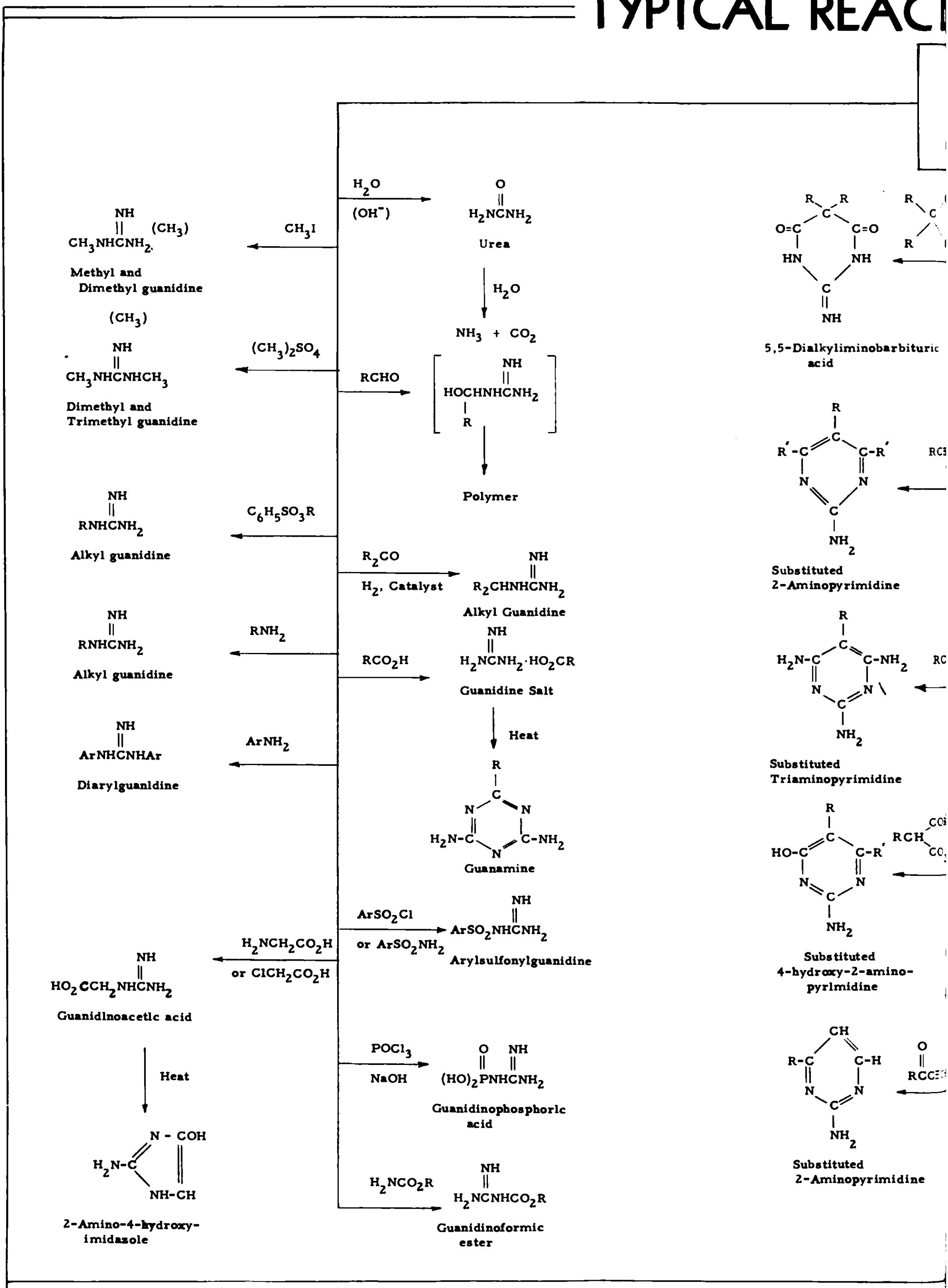
(c) The alpha, beta-unsaturated carbonyl structures,



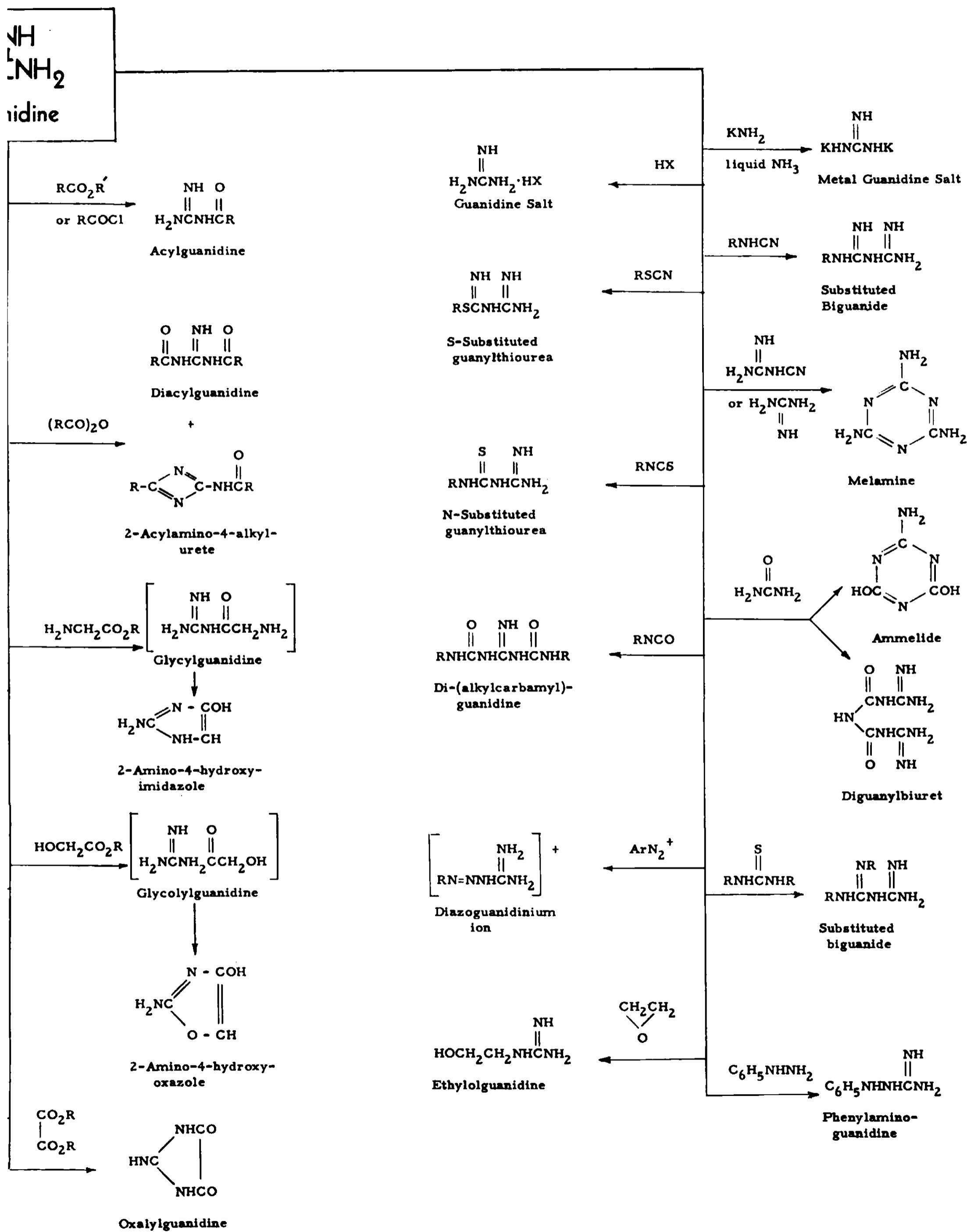
(a) The beta, beta-dicarbonyl structure

Dialkyl malonic esters (51, 247c, 296, 297, 302, 319, 391, 408), acids (30), and acid chlorides (148, 293) have been used to prepare the chemotherapeutically important 5,5-dialkyliminobarbituric acids.

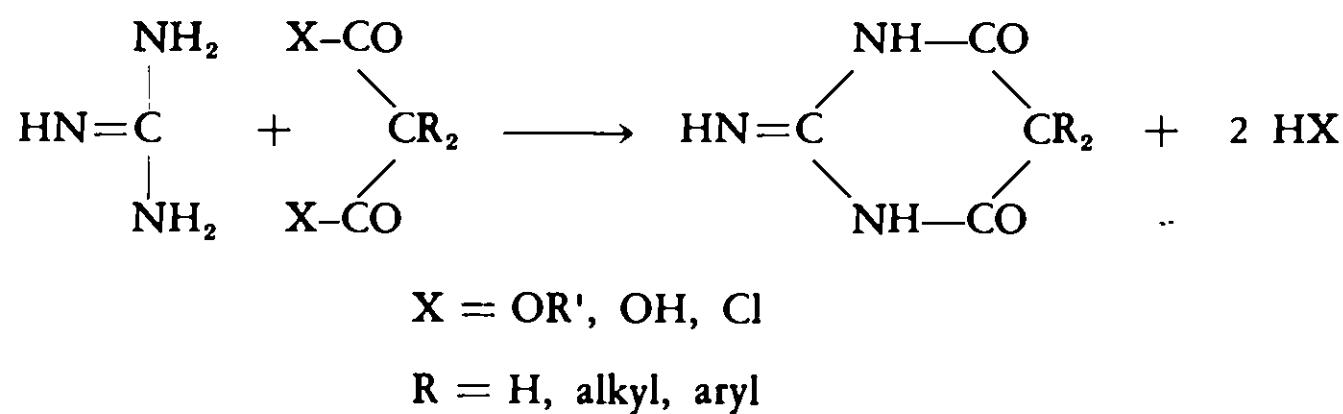
TYPICAL REACT



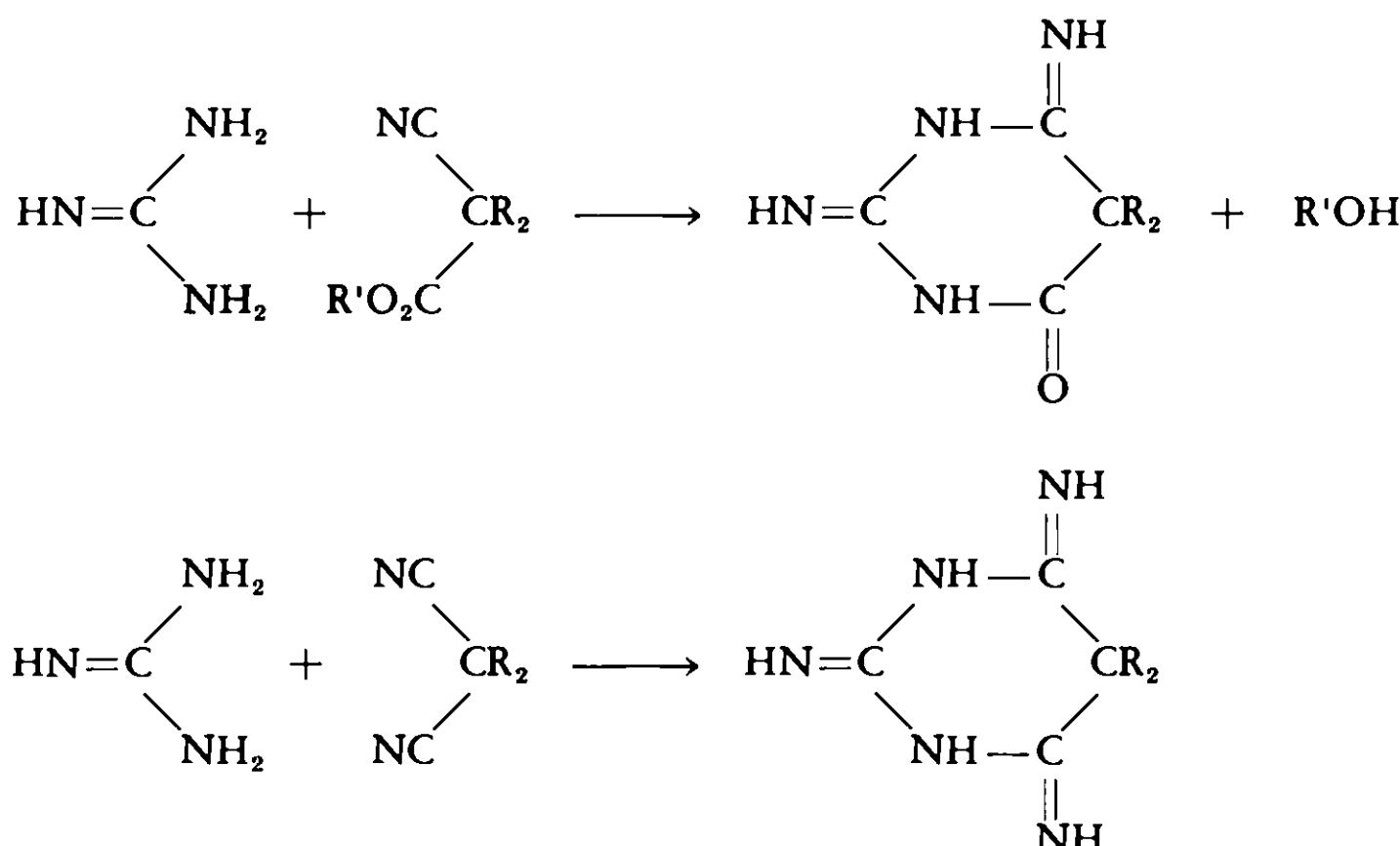
CONFORMATIONAL ANALYSES OF GUANIDINE



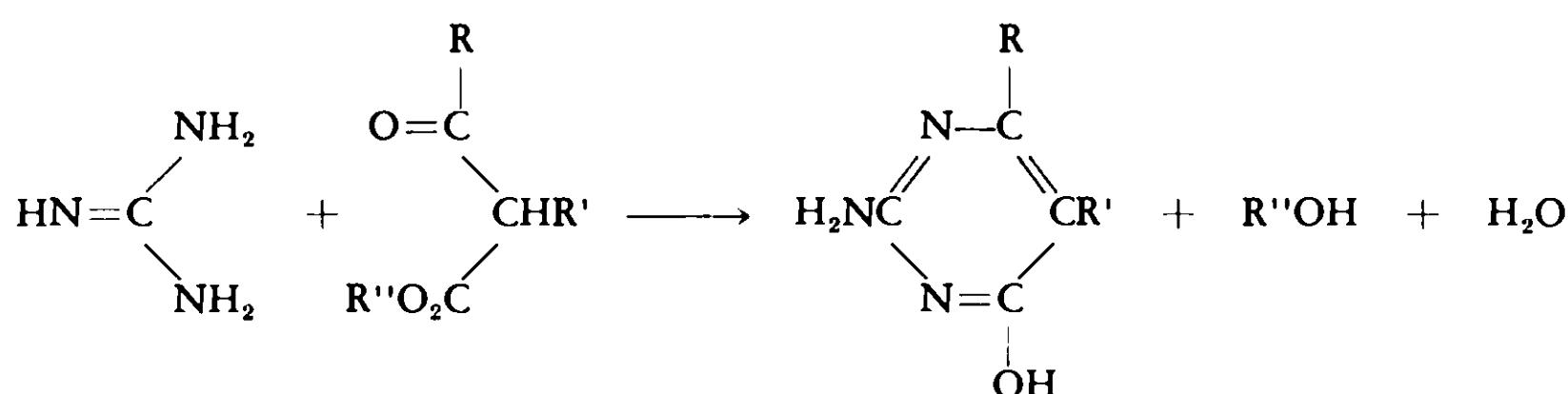
NITROGEN CHEMICALS DIGEST



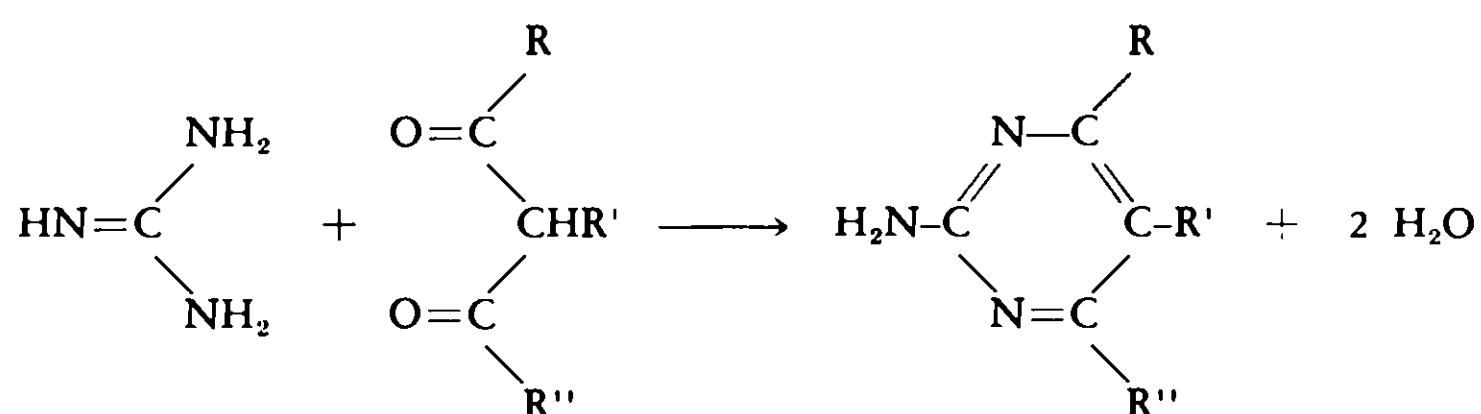
Diamino- (36, 292, 451) and triaminopyrimidine (294, 452) derivatives are obtained from substituted alpha-cyanoacetates and malononitriles, respectively.



With beta-keto acids (376), acid chlorides (291) and esters (38, 48, 51, 70, 95, 131, 210, 213, 236, 237, 247a, 321, 384, 488) in alcoholic sodium ethylate one may introduce substitution at the 4- and 5-positions of the pyrimidine ring.



Malonaldehydes (214, 235, 392), alpha-formyl ketones (41, 235), and 1,3-diketones (51, 141, 210, 282) have been used to prepare alkylated 2-aminopyrimidines similarly.

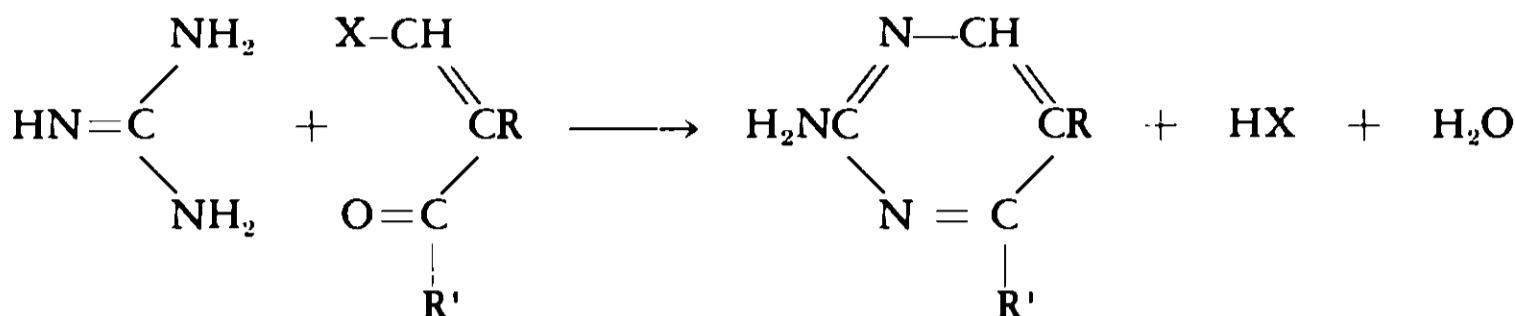


NITROGEN CHEMICALS DIGEST

(b) The Beta-substituted Carbonyl Structure



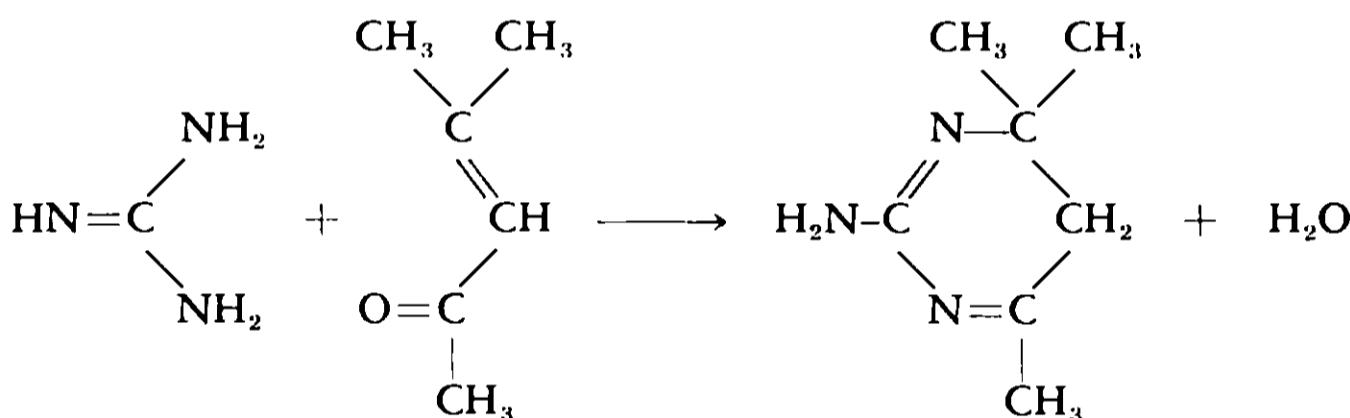
Compounds having the general structure $\text{X}-\text{CH}=\text{CH}-\text{C}(=\text{O})-\text{R}$ will form 2-aminopyrimidines on treatment with guanidine.



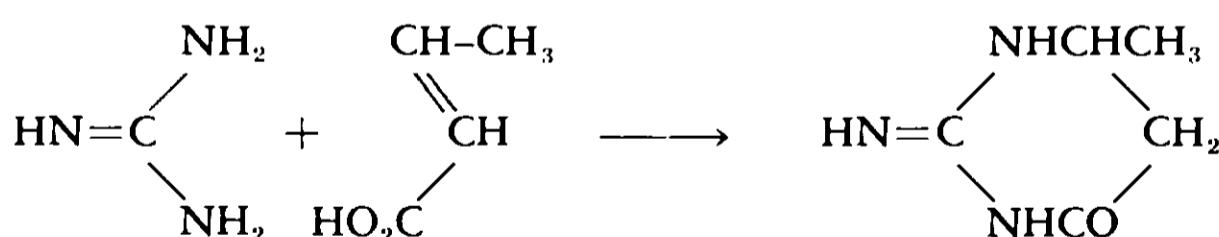
Among the reagents which have been used in this manner are anthranilic acid (256), 1,1-dicarbethoxy-2-ethoxyethylene (306), the diethyl acetal of beta-ethoxyacrolein (247e, 308), and 1,1,2,3-tetrachloropropylene (247d), this latter material containing a latent carbonyl group.

(c) The alpha, beta-unsaturated carbonyl structure

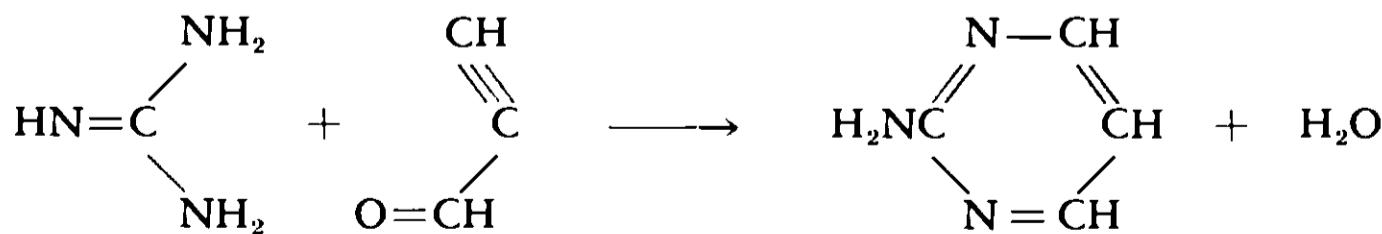
Pyrimidines have been synthesized by the condensation of guanidine with compounds of the structure $\text{R}'\text{CH}=\text{CHCOR}''$, such as ethyl cinnamate, phorone or mesityl oxide (456).



Acrolein and cinnamyl aldehyde failed to yield isolatable products (456), but crotonic acid gave a tetrahydro-iminopyrimidone (334).

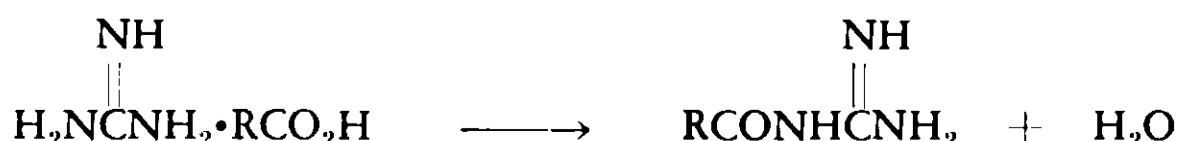


Carbonyl compounds with an alpha, beta-triple bond, such as propargyl aldehyde (192, 247f), 1-butyn-3-one (353), and diethyl acetylene dicarboxylate (383) readily condense with guanidine.



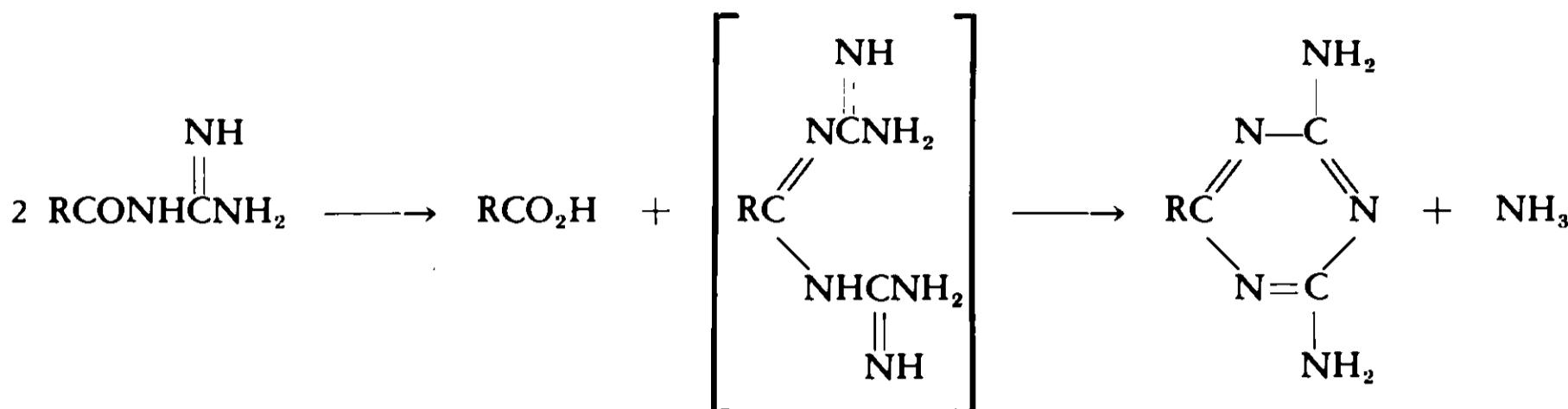
(3) GUANAMINES

In 1874 Nencki (317) reported that guanidine acetate lost ammonia and water on heating to 200-230°C. and was thereby converted into acetoguanamine. Since it is known that acylated guanidines may be converted to guanamines by heating above their melting point (406), it seems likely that acylation may be the first step in the reaction under discussion.



NITROGEN CHEMICALS DIGEST

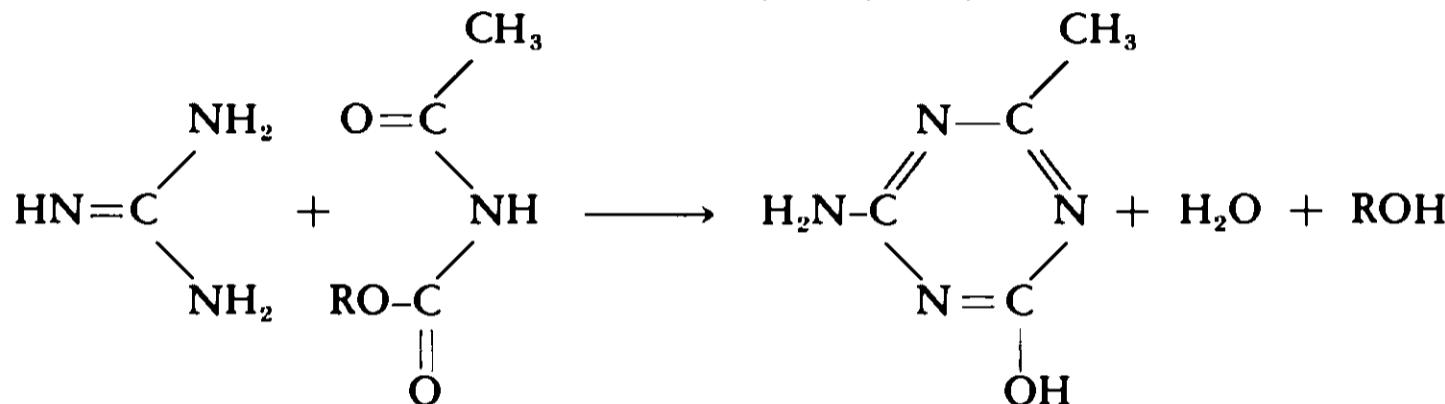
An unstable N,N'-diguanyl amidine is thought to be the next intermediate in this guanamine synthesis (471).



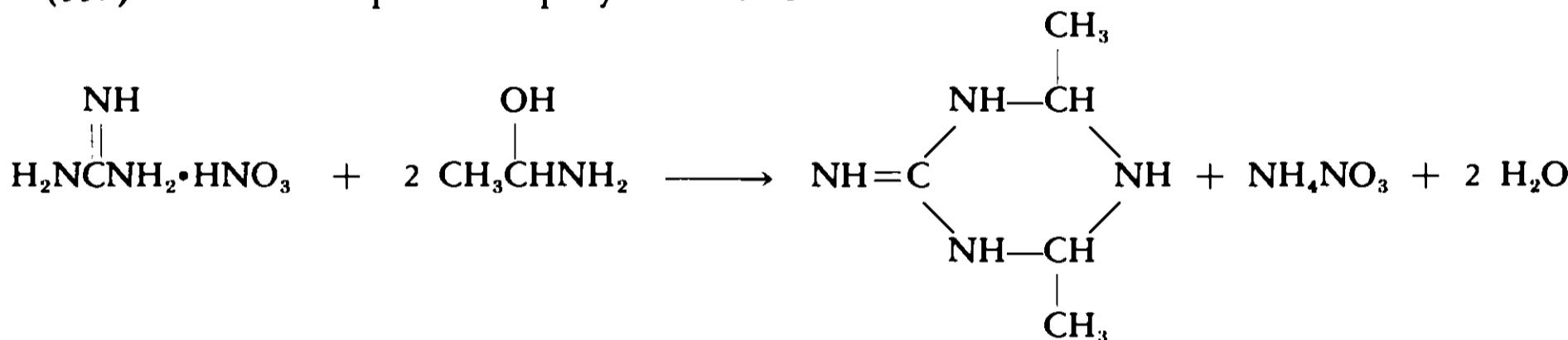
A large number of guanamines have been prepared in this manner (179).

(4) OTHER TRIAZINES

Triazine derivatives may occasionally be prepared by the methods which are useful for pyrimidine formation. Acetylurethane and guanidine condense to form 2-methyl-4-hydroxy-6-amino-1,3,5-triazine (330).



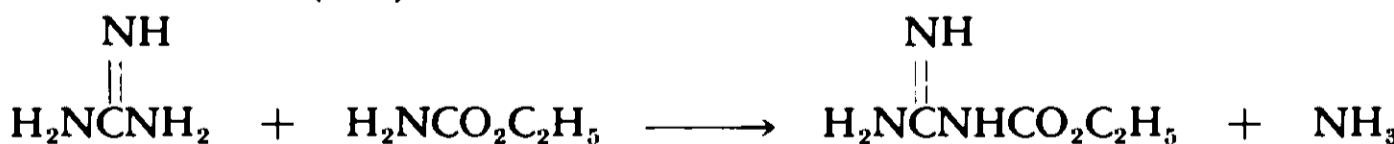
Recently, hexahydrotriazines have been successfully prepared from moist aldehyde-ammonia and guanidine nitrate (335). The reaction proceeds rapidly at 70-75°C.



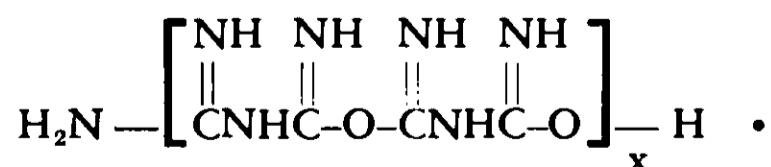
The formation of other triazine derivatives is discussed below.

REACTION WITH CARBAMATES

On heating a mixture of ethyl carbamate and guanidine carbonate at temperatures below 110°C., one obtains ethyl guanidino-formate (472).



At higher temperatures (120-310°C.) a linear polymer is formed. The structure of this material is proposed (472) to be



REACTION WITH CYANAMIDES

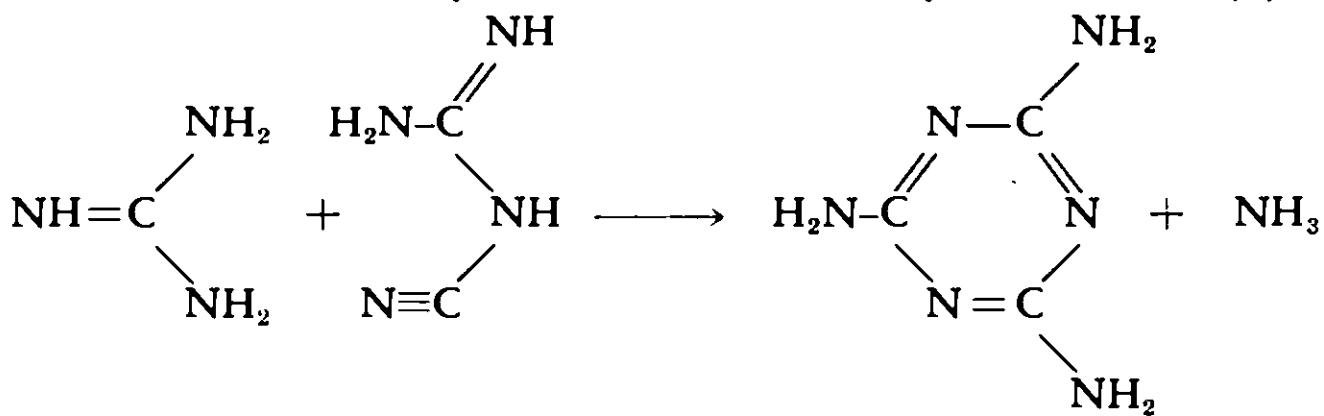
Guanidine reacts with mono- (219, 361) or di-alkyl cyanamides (396) to form substituted biguanides. However, no reaction takes place with unsubstituted cyanamide (364, 366).



NITROGEN CHEMICALS DIGEST

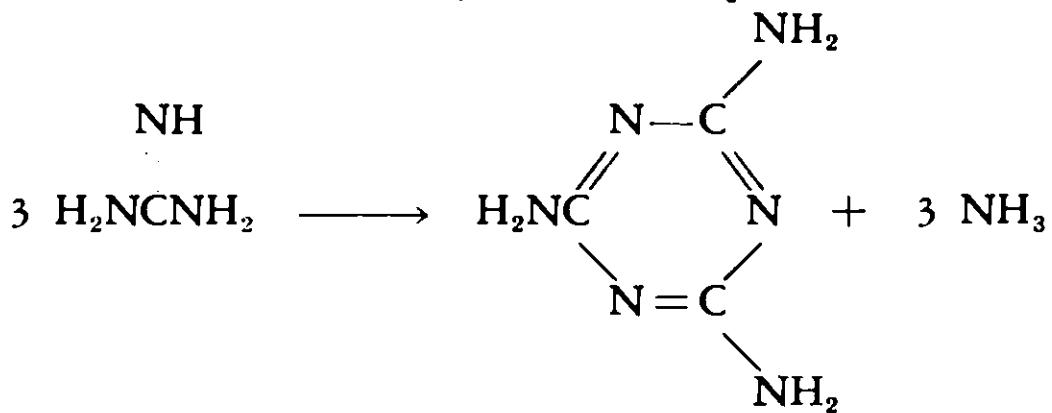
REACTION WITH DICYANDIAMIDE

Guanidine carbonate reacts with dicyandiamide at 200°C. to yield melamine (4).

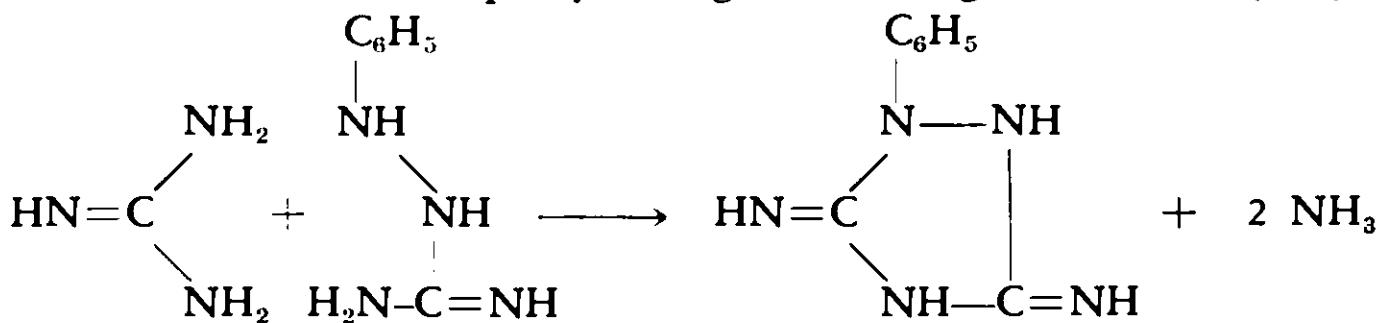


REACTION WITH GUANIDINES

When free guanidine is heated in a closed vessel at high temperatures, melamine is formed (78). Similarly, guanidine carbonate is converted to melamine by heating in aqueous ammonia (102).

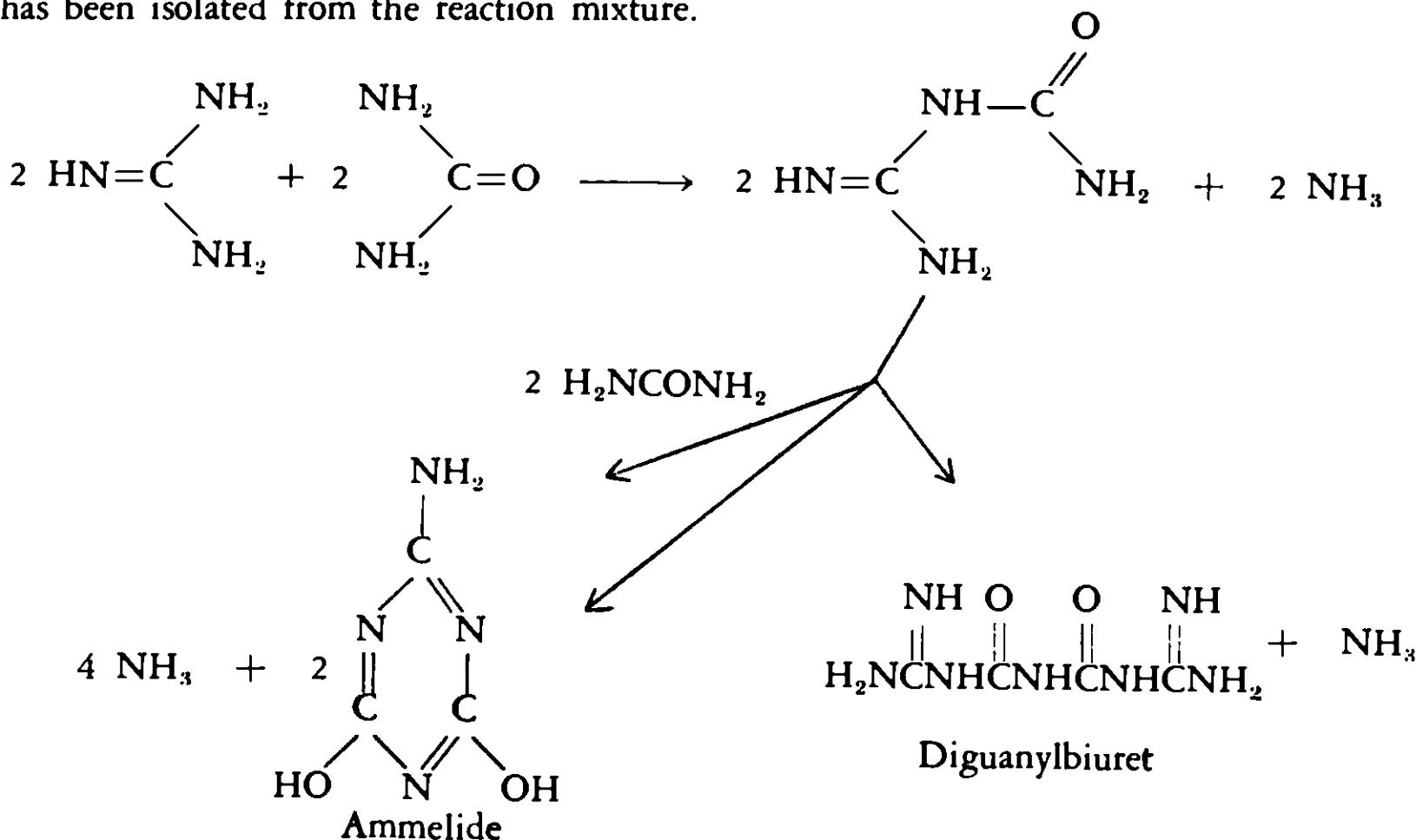


Guanidine has also been condensed with phenylaminoguanidine to give a triazole (343).



REACTION WITH UREAS

It is said that the fusion of urea and guanidine can be controlled to yield either ammelide or diguanylbiuret (414). If four moles of urea are heated with one mole of guanidine only ammelide is obtained. With two moles of urea both ammelide and diguanylbiuret are produced; but with equimolar quantities of the two reactants the reaction yields only the biuret. The mechanism (414) apparently involves the intermediate formation of guanylurea which has been isolated from the reaction mixture.

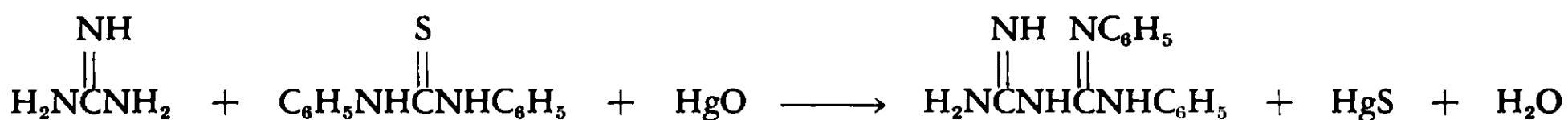


NITROGEN CHEMICALS DIGEST

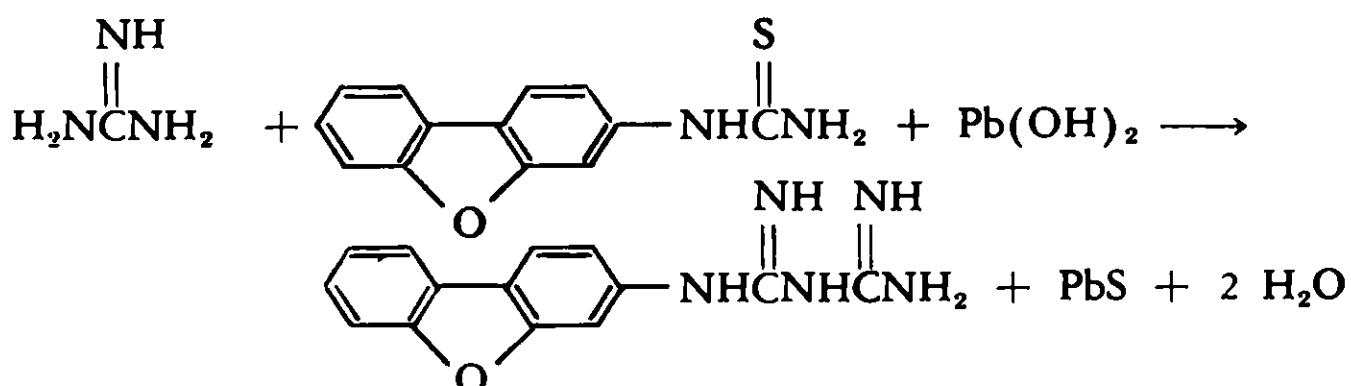
Diguanylbiuret is said to result also from the fusion of acetylurea with guanidine (363).

REACTION WITH THIOUREAS

In the presence of mercuric oxide guanidine and thiocarbanilide react to give an unsymmetrical diphenylbiguanide (92).

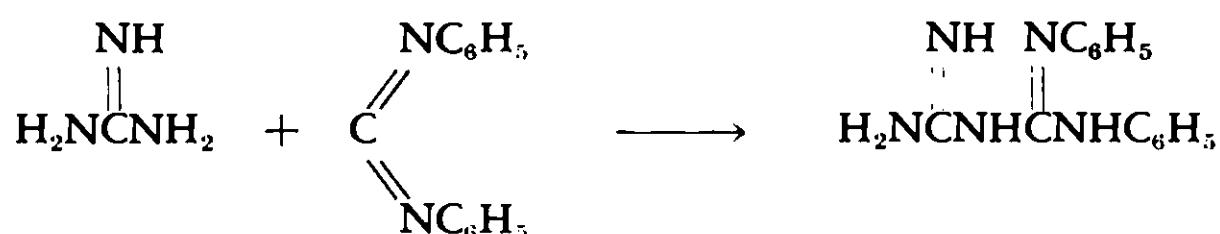


Some interesting biguanides have been made by Puetzer (360) by this reaction:



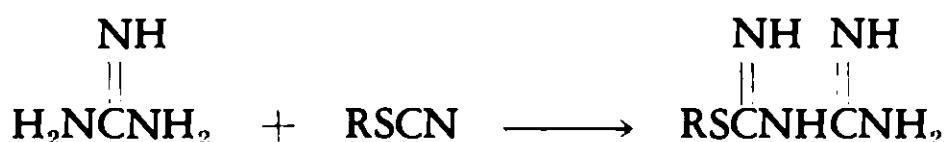
REACTION WITH CARBODIIMIDES

Biguanides have been prepared from carbodiimides and guanidine (92), but low yields make this a poorer preparative method than that using thioureas.



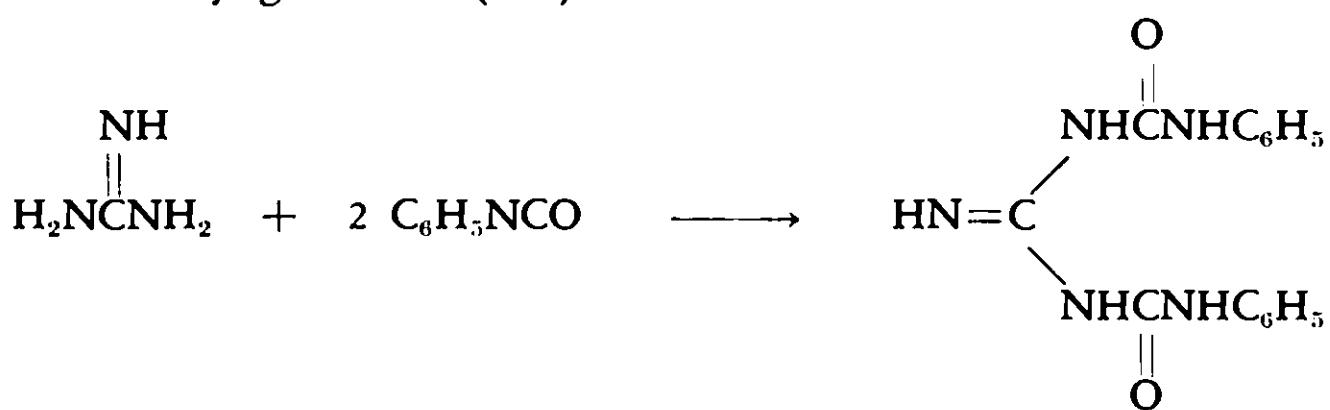
REACTION WITH THIOCYANATES

Guanidine reacts with alkyl thiocyanates to form S-alkyl guanylthioureas (219, 359).



REACTION WITH ISOCYANATES

Guanidine salts react vigorously with isocyanates in the presence of sodium ethylate (9, 298) to give symmetrically substituted dicarbamyl guanidines (410).



REACTION WITH ISOTHIOCYANATES

Guanidine adds to phenylisothiocyanate at 100°C. to yield phenylguanylthiourea (92, 298).

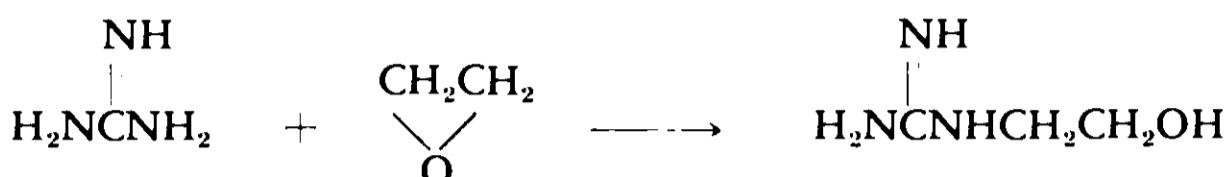


NITROGEN CHEMICALS DIGEST

This reaction is said to be general for isothiocyanates (411), the products being, in every case, the monosubstituted product instead of the di-substituted product as obtained from guanidine and isocyanates (410).

REACTION WITH ALKYLENE OXIDES

Guanidine and its salts react with ethylene oxide to form monoethylol guanidine and other viscous or resinous products (135).



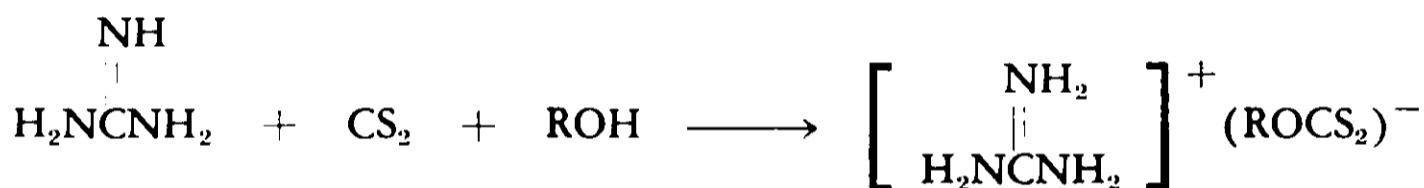
The reaction at 10°C. is quite exothermic.

REACTIONS WITH CARBOHYDRATES

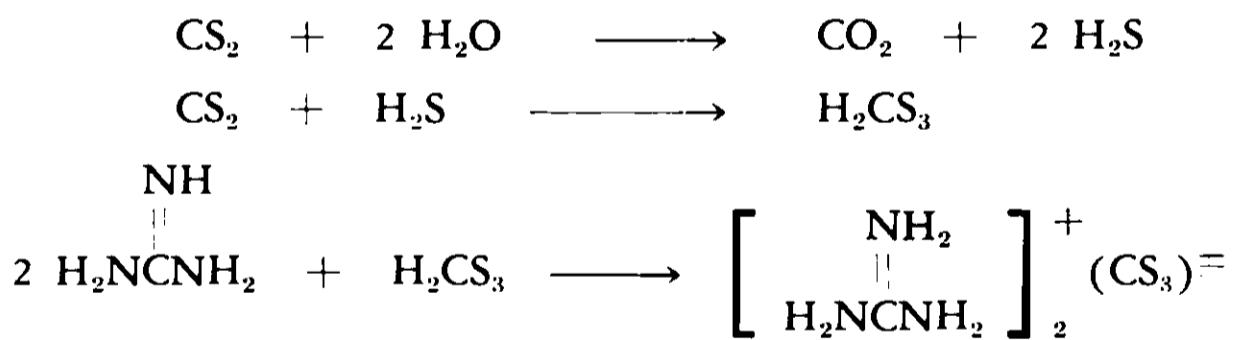
Addition compounds with guanidine have been obtained from hexoses (311), polysaccharides and starches (109, 357). It has been reported that guanidine will catalyze the formation of strongly reducing di-enol sugars from hexoses (464). With large excesses of guanidine, glucose can be made to polymerize (487), the result being similar to that obtained by treating glucose with strong caustic solutions. The formation of condensation polymers of guanidine and various carbohydrates has been reported (138).

REACTION WITH CARBON DISULFIDE

Guanidine xanthates result from the treatment of guanidine with carbon disulfide in alcohol solutions (229, 287).

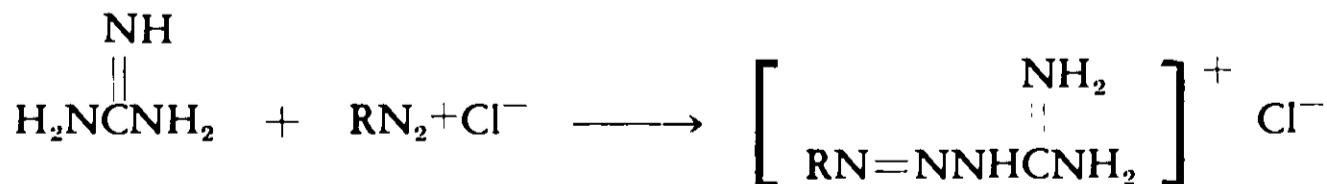


In aqueous solution guanidine trithiocarbonate results from this reaction (424). The mechanism is said to be as follows:



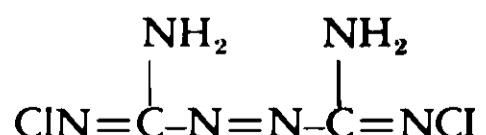
REACTION WITH DIAZONIUM SALTS

Diazonium salts readily couple with guanidine in neutral solutions (86, 468) to form products believed to be N-diazoguanidinium salts.



REACTIONS WITH OXIDIZING AGENTS

Chlorine (242), bromine (242), iodine (367) and cyanogen (297) react with guanidine to give indefinite and unidentified products. The chlorination product might have a diazo structure (394).

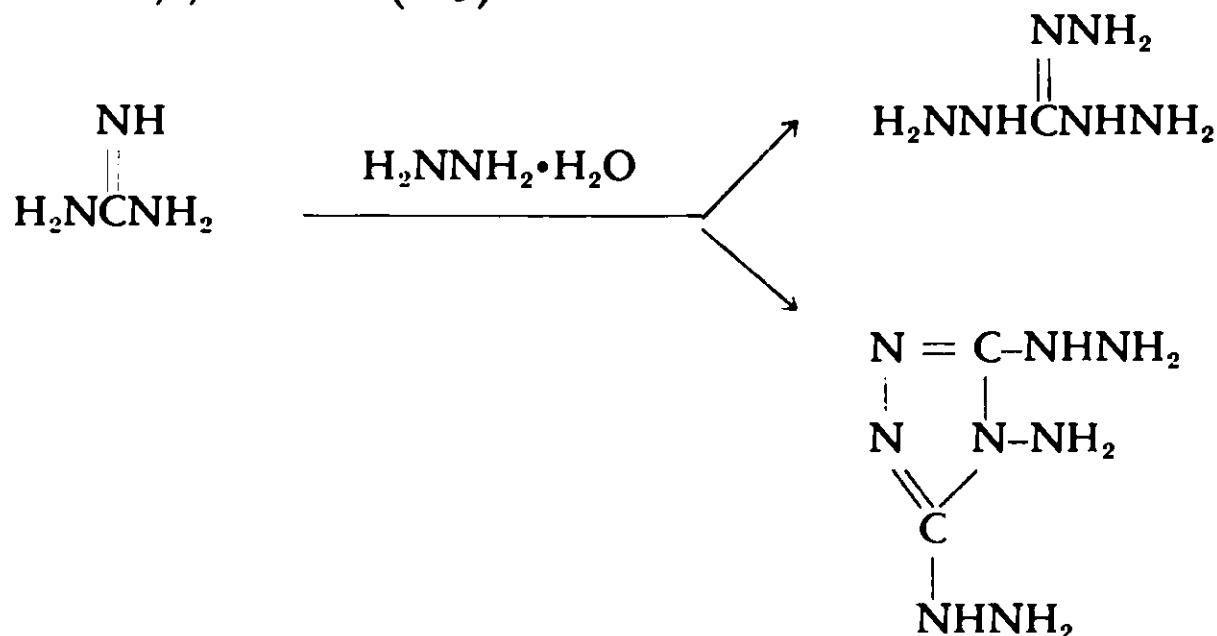


This same product is also obtained from the reaction of hypochlorite with guanidine (85, 394). Hypobromite oxidation completely destroys the molecule, liberating nitrogen (87, 108).

Guanidine is decomposed to nitrogen by the action of other oxidizing agents: potassium dichromate (84), perbenzoic acid (50) and air or nascent oxygen in the presence of pentacyanoferrate ion (32). The electrolytic oxidation of guanidine has been studied (60).

REACTION WITH HYDRAZINES

Guanidine salts react with hydrazine hydrate to give two reaction products: triaminoguanidine (344) and 4-amino-3,5-dihydrazino-1,2,4-triazole (423).

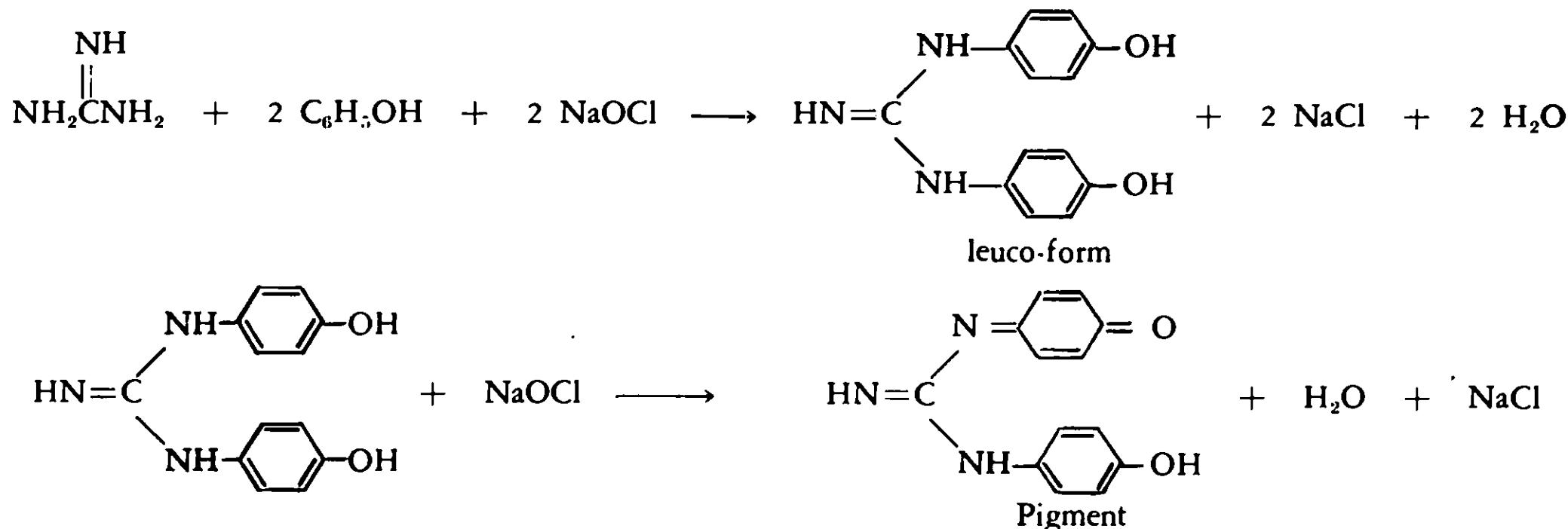


This latter product is said to be a powerful reducing agent, reducing ammoniacal silver in the cold and decolorizing iodine solutions. With phenyl hydrazine, the reaction is much slower and stops at the mono-substitution stage (342).



REACTION WITH PHENOLS

Yellow pigments are formed when phenols are reacted with guanidine in the presence of hypochlorite (145). This reaction has been used for the qualitative detection of guanidine.

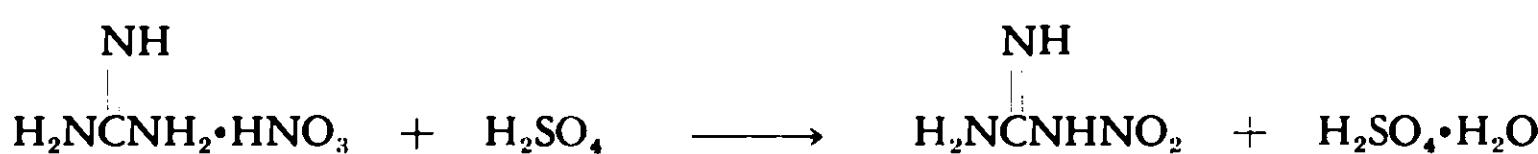


REACTIONS WITH PROTEINS

Guanidine salts form addition products with egg albumen, gelatine, casein and globulin (176) and with nucleic acids (475). Under proper conditions they may also cause degradation of the proteins (174).

NITROGUANIDINE PRODUCTION

In 1879 Jousselin (239) dissolved dry guanidine nitrate in fuming HNO_3 and passed nitrous oxide through this solution. On drowning with water, he obtained a precipitate of "nitrosoguanidine." Several years later Thiele (437) showed that this product was actually nitroguanidine. Thiele also prepared this material by dehydrating guanidine nitrate with sulfuric acid (437).



The sulfuric acid process has since become the preferred way of preparing nitroguanidine (151, 333, 341, 395, 413, 419, 490), although phosphoric acid is also effective (106).

POTENTIAL APPLICATIONS

Guanidine, its salts, and its simple derivatives have been used or their use suggested in a wide variety of fields. The more important applications of these compounds are described in this section.

AGRICULTURE

A variety of inorganic guanidine salts have proven acceptable as fertilizers (7, 61, 200, 263, 266, 449). Other derivatives have been tested as root-growth inhibitors (440).

ANALYTICAL CHEMISTRY

Aryl guanidines (442) and guanidine carbonate (115) have received attention as acidimetric and alkali-metric standards. Guanidine oxalate may be used in the separation of calcium from barium and strontium (28). Nitrosoguanidine has been used for the qualitative detection of nickel, ferrous, palladium and other cations (252); guanidine itself for nitrate ion (418), and benzoyl guanidine for naphthylaminesulfonate anion (346).

ANTIOXIDANTS AND PRESERVATIVES

Guanidine compounds have found considerable use as antioxidants for textiles (415), soaps, fats, oils, etc. (5, 139, 149, 314, 405); as stabilizers of aldehydes (328, 466), aromatic amines (375), alkylene glycols (55), alkali percarbonates (467), chlorinated hydrocarbons (73, 305), metallic driers (65), and various polyvinyl plastics (91, 484); and as inhibitors of corrosion by anti-freeze mixtures (188), of tarnishing of silverware (384), and of metal dissolution by pickling acids (198). Derivatives of guanidine have been discussed as antioxidants (480) and as preservatives (458) for rubber. Diaryl guanidines act as paint antioxidants (216), enamel preservatives (173) and as paint-livener inhibitors (409).



CATALYSTS IN CHEMICAL PROCESSES

Guanidine hydrochloride has been substituted for ammonium chloride in the catalyst for the conversion of acetylene to vinylacetylene (320, 426).

CHEMOTHERAPY

The great value of sulfaguanidine (288) and sulfadiazine (376) as modern "wonder-drugs" is well known. The therapeutic uses of many other guanidine compounds have not been so widely publicized, although they have been found to be very useful in the treatment of a number of diseases, including trypanosome infections (157, 227, 230, 272, 378, 421), schizophrenia (280) and muscular dystrophy (117, 276, 349, 441). Guanidine derivatives have shown activity as antihistaminic agents (228), as protectives against anaphylactic shock (67), as hypnotics (302), as anaesthetics (139, 160, 399, 447), as analgesics and antipyretics (410), and as bactericides, antiseptics, disinfectants and the like (133, 156, 163, 219, 262, 358, 359, 360, 361, 378, 394, 399). Considerable activity has centered about the use of guanidine derivatives as antimalarials (93, 94, 323, 340, 446, 481) and as insulin substitutes (14, 52, 267, 270, 273, 351, 355, 356, 368, 402).



DYESTUFFS

Guanidine compounds are reported to be of value as intermediates and additives for azo dye compositions (99, 143, 241, 275), vat dyes (162, 220), spirit-soluble dyes (72), sulfur dyes (77), metachrome dyeing baths (303, 380), and various other dye preparations (31, 35, 348, 370, 482). Some guanidines act as precipitants of acid and oxy azo type dyes (120, 428, 457). Guanidine-formaldehyde resins may be used to increase the fastness of dyes and prints (478), and to lend printing pigments an affinity for glass fabrics (286).



ELECTROPLATING

Guanidine hydrocyanide may be used in aqueous silver-plating baths in place of sodium or potassium cyanide (165).

EXPLOSIVES

Various nitrated guanidine derivatives, particularly nitroguanidine, are excellent explosives (103, 127, 172, 180, 271, 285, 326, 419, 445). The special value of nitroguanidine is due to its ability to produce a flashless and relatively cool explosion, making it valuable as a military propellant powder (172). Several guanidine salts have also been used in explosive mixtures, among them guanidine nitrate (285), picrate (327), chlorate (287), and perchlorate (75, 287). "Tetrazene" (guanylnitrosoaminoguanyl tetrazene) (68, 420), lead nitroaminoguanidine (15, 82, 347) and other tetrazoles (207) make excellent primers. Special mixtures of guanidine explosives have been developed for such purposes as blasting (83, 381, 460), exploding rivets (194), and rocket propulsion (434).

FLUXING AGENTS

Guanidine salts are useful as fluxing agents in the conversion of cyanamide or dicyandiamide to melamine (59).

GLASS

If pulverized glass is mixed with a finely divided material containing a guanidine salt and heated for a sufficient time to soften, coalesce and form a multiplicity of bubbles, and then cooled, a multicellular glass is produced (217).

GRAPHIC ARTS

A variety of simple guanidine salts may be used to improve photographic developing solutions (183, 184, 218, 229) and fixing baths (25, 182). In photographic emulsions guanidine derivatives may act as sensitizers (129, 249), anti-static (313) or coloring agents (8). Guanidine ferro- and ferricyanides are useful in the preparation of blueprint papers (26, 268). Other derivatives may be employed in the preparation of diazo ice-colors (261), in the production of tell-tale color reactions on bank checks and the like (412), or to increase the water resistivity of diazo type layers. (416).



INSECTICIDES, FUNGICIDES, AND PESTICIDES

Several guanidine derivatives are valuable as moth-larvae repellents (26, 189, 268), mothproofing agents (76, 190, 231, 301, 309, 486), general insecticides (133, 137, 185, 300), rodenticides (113, 287), fungicides (133, 171, 185), and parasiticides (186). Salicylalaminoguanidine can be used to stabilize DDT against thermal decomposition (177).

LEATHER

Some sulfur-containing guanidines may be used as leather dehairing agents (229, 232).

Alkylol guanidines (139) and alkyl alkylol guanidines (134) are leather finishing agents.

METALLURGY

Various guanidines are active as froth flotation agents for sulfide ores (229, 417), for sylvite (248), for zinc blende (29) and for the separation of acidic from basic minerals (234).

PAPER

It is reported (33, 100) that guanidine salts are effective fluidizing agents for starch. Experimental results (9), summarized in Figure 9, show that they are more efficient in this respect than dicyandiamide which is, in turn, two to five times as effective as urea. Guanidine phosphate is useful as a flame-retardant when applied to paper (9).

PERFUMES

Violet perfumes may be purified with the help of aminoguanidine (387).

PETROLEUM

Guanidine soaps increase the lubricating quality of mineral oils (429) and stabilize water-in-oil emulsions (53).

PLASTICS, PAINTS AND SURFACE COATINGS

The literature records several patents which involve the production of thermosetting resins from guanidine and aldehydes, particularly formaldehyde, either with or without the addition of other reactant molecules (16, 17, 19, 125, 208, 209, 385, 422, 435, 474). Special modifications of the basic process have been developed to

produce anion (27, 47, 123, 195, 431) or cation (371) exchange resins, as well as resins for the finishing treatment of paper stock (18), glass (377) and textiles (see below). Guanidine salts may be useful as regenerating agents for anion-exchange resins (175). Guanamines (from acyl guanidines) may be used to make thermosetting resins (406), or they may be employed as accelerators for various surface-curing compositions (377). Molding resins have been prepared from guanidine-shellac mixtures (97, 400) and from guanidines and acrylonitrile (124). Halogenated acyl guanidines act as accelerators for self-curing amino plastics (96). Various guanidine salts may be employed in the plastic industry as catalysts for urea-formaldehyde resin formation (88), and as accelerators for the production of mixed nitro-fatty acid esters of cellulose (479). Synthetic fibers have been produced from guanidine-glycol polymers (121). Diaryl guanidines are useful as flame-retardants for nitrocellulose plastics (432), and in the preparation of certain pigments (185). Methanol solutions of guanidine carbonate may be used to hydrolyze polyvinyl acetate. (62)

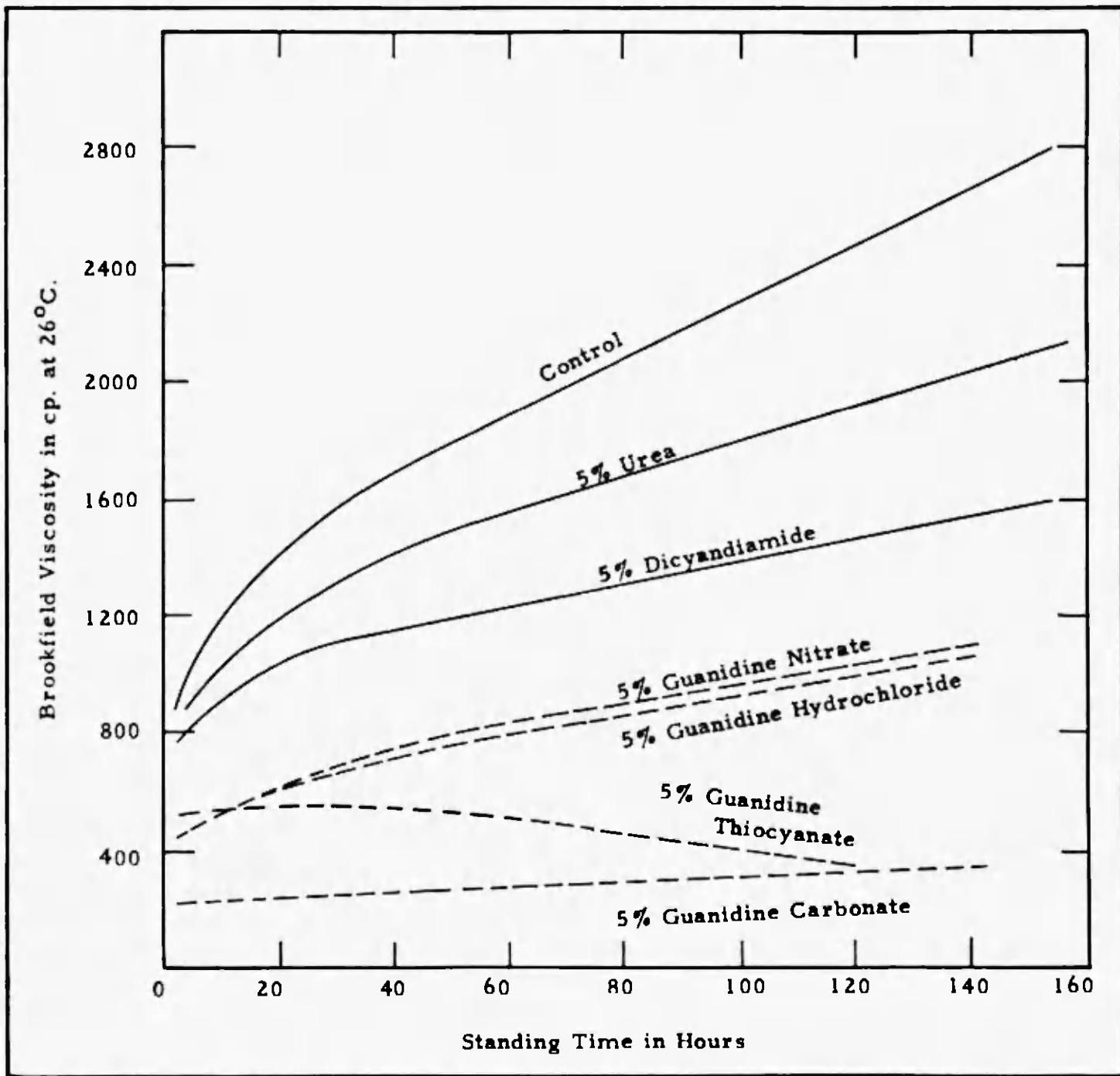


Figure 9—The Viscosity of 20% Dispersions of a Typical Chlorinated Starch Modified with Guanidine Salts (9)

PROTEINS

Keratin proteins are dispersed by guanidine hydrochloride (238). Relaxation of keratin fibers occurs on treatment with guanidine bisulfite, so this material has been proposed as a permanent waving agent (299). Guanidine carbonate solutions can be used to purify casein (80). Under proper conditions guanidine salts may be used to cause protein degradation (174).

RUBBER

In 1922 Weiss stated that diphenyl guanidine is an excellent vulcanization accelerator (470). The use of this and other aryl guanidine derivatives as vulcanization accelerators and plasticizers of synthetic rubbers has attained such proportions that this is now one of the most important single uses of guanidines in industry.

(Although there is no recent and comprehensive review of this subject, the reader's attention is called to discussions contained in references 315 and 316.) Among the guanidine derivatives which have found use as vulcanization accelerators may be mentioned the diaryl guanidines (63, 98, 336, 398), diphenyl guanidine phthalate (404), and a zinc chloride adduct of di-(orthotolyl) guanidine (AERO AC-50*) (104).

Diazoguanidines have been suggested as a source of nitrogen in the preparation of closed-cell, gas-expanded rubber (86).

SOAPs

Additional interesting features of guanidine derivatives are found in the properties of guanidine soaps. Fatty acid salts of guanidine are excellent emulsifying agents and therefore should find considerable use as soap and detergent additives (136, 191, 202, 265, 350). The synthesis of guanidine soaps as described by Poliakoff and Smith (350) is simple, practical, and capable of producing almost theoretical yields of soap. Essentially it involves reacting a fatty acid with guanidine carbonate in ethanol or acetone.

Measurements of the practical washing ability indicate that the guanidine soaps are about as good as sodium and potassium soaps for laundry use (350). The deflocculating power was found to be 445% greater and the emulsification power 20% greater than those of the alkali soaps (350). Guanidine soaps have the added advantage that they do not discolor white fabrics.

Alkyl (215) and alkylol (7, 134, 135, 220) guanidines also have excellent detergent properties. Guanidine derivatives may be used to break water-in-oil emulsions (34, 107).

SYNTHETIC DETERGENTS

Novel properties of guanidine carbonate are its ability to reduce the hygroscopicity and to increase the detergency of certain synthetic surface active agents (9).

Detergents of the sodium alkylaryl sulfonate class are often extremely hygroscopic at 50% R.H. and above. The addition of as little as 5% to 20% of guanidine carbonate on the weight of sodium alkylaryl sulfonate mix (normally containing 40% active ingredient and 60% sodium sulfate) will eliminate the hygroscopicity completely giving stable free-flowing products. The quantity of guanidine carbonate required increases with the relative humidity to be tolerated. The data (9) in Table IV show the amount required to maintain free-flowing powders at various humidities at 40°C.



TABLE IV
Effect of Guanidine Carbonate on Hygroscopicity

Guanidine Carbonate Based on Wt. of Sodium Alkylaryl Sulfonate %	R.H. Tolerated at 40°C. %
0	35
1	55
2	60
5	70
10	85-90
12	90-95
15	95-99

All concentrations wet at 100% R.H.

Guanidine carbonate can be incorporated both by simple dry blending and by mixing with the neutralized surface-active agent in the wet state before drying. Thus it is not necessary to coat the surface active agent particle to decrease its hygroscopicity as is true with hygroscopicity-control agents such as clay, tricalcium phosphate, talc, etc.

In addition to decreasing hygroscopicity, guanidine carbonate and sulfate, as well as other guanidine salts, greatly improve the washing action of sodium alkylaryl sulfonates on wool. This property is illustrated by the pictures in Figure 10 and the data (9) in Figure 11. Maximum enhancement of detergency on wool is obtained

* Reg. U.S. Pat. Off.

NITROGEN CHEMICALS DIGEST

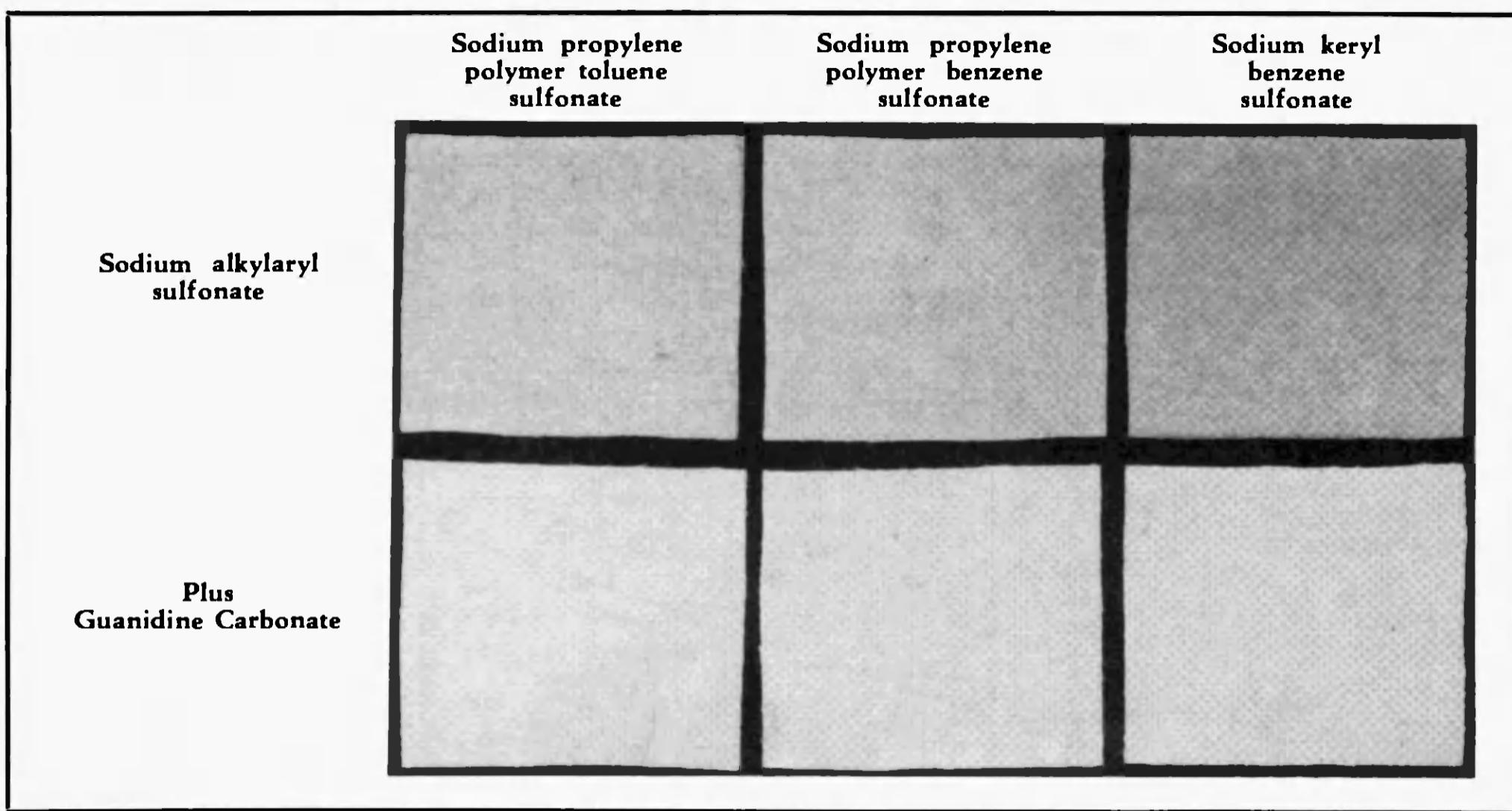
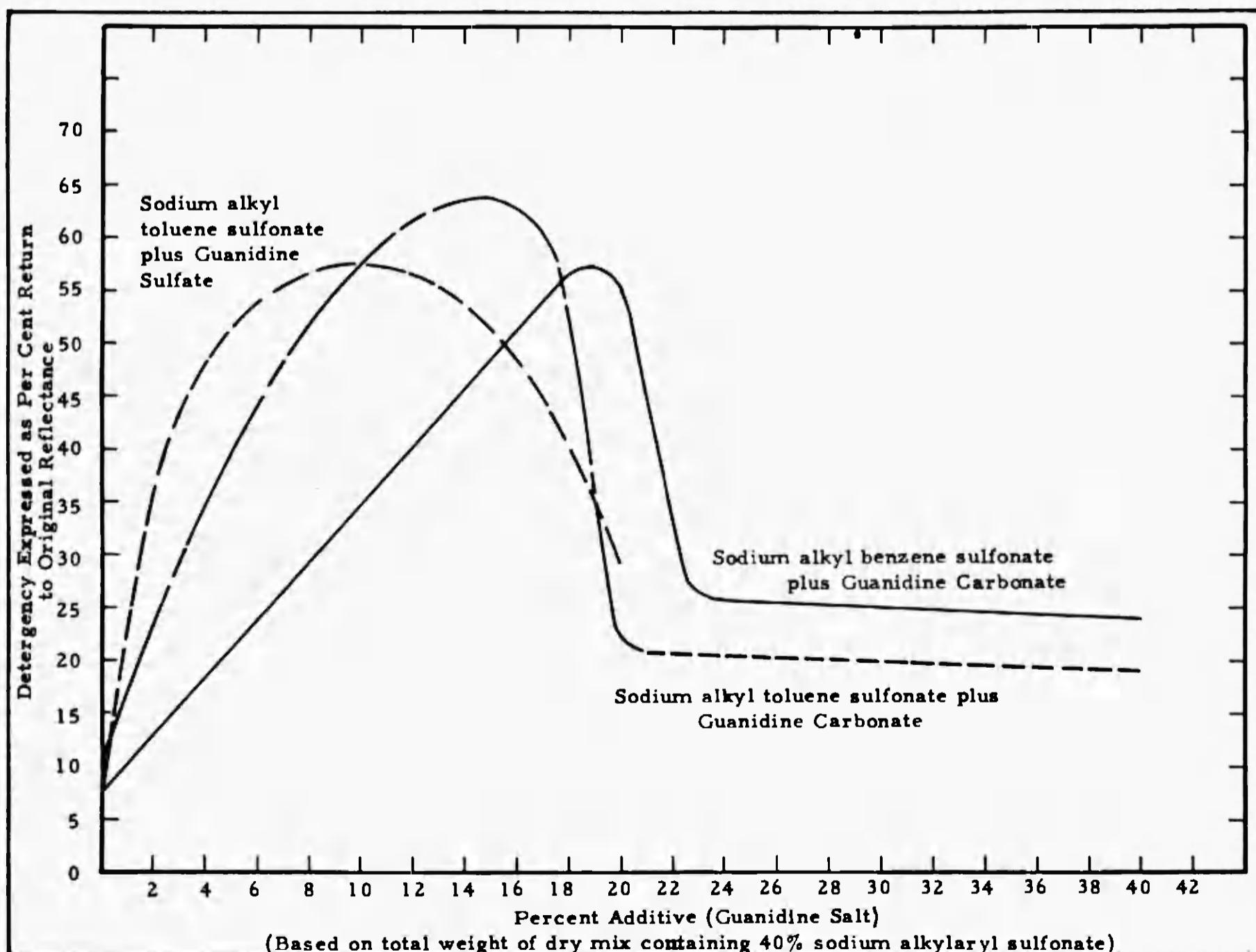


Figure 10—Effect of Adding 5% by Weight of Guanidine Carbonate to Sodium Alkylaryl Sulfonates (40% Active + 60% Na_2SO_4) on Wood Detergency at 110° F.



NITROGEN CHEMICALS DIGEST

with 10-15% of guanidine carbonate or sulfate on the weight of detergent mix. Larger quantities of these guanidine salts cause less increase in detergency until, with 20% guanidine salt, the detergency is lowered almost to that of the detergent to which no guanidine salt was added.

The concentration of guanidine carbonate needed to obtain maximum detergency for two different types of sodium alkylaryl sulfonates, i.e., alkyltoluene and alkylbenzene, is not the same (see Figure 11). Therefore the optimum amount of guanidine carbonate required must be determined for each new detergent.

The detergency of sodium alkylaryl sulfonates on cotton is not increased by the use of guanidine salts to the same extent as on wool (Figure 12). For washing artificially soiled cotton percale 20% guanidine carbonate on the weight of detergent is required to increase the detergency by approximately 15%, whereas 5% guanidine carbonate has little or no effect.

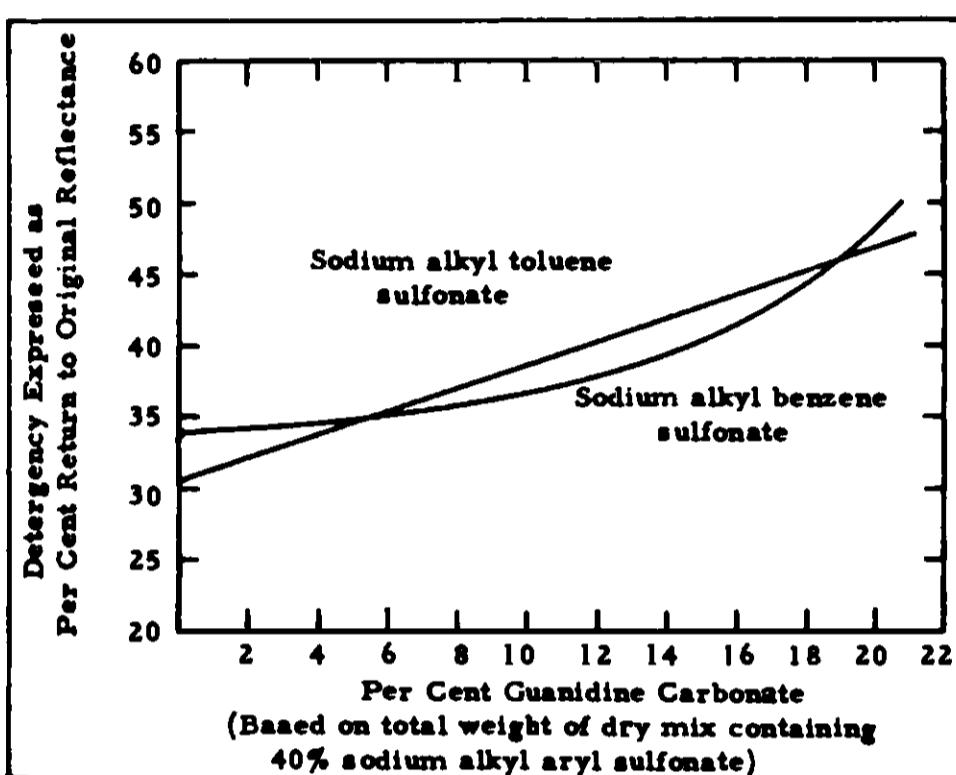


Figure 12—Effect of Guanidine Carbonate on Detergency of Sodium Alkylaryl Sulfonates on Cotton

In certain instances it was observed that the guanidine carbonate increased the rate with which sodium alkylaryl sulfonates could be drum dried.

By the use of guanidine carbonate an increase in the wool detergency of most sodium alkylaryl sulfonates may be expected as is shown in Table V. However, it is also evident from Table V that guanidine carbonate is not as effective for increasing the washing properties of all types of detergents.

TABLE V
Effect of Guanidine Carbonate on Detergency

Detergent*	Active Ingredient %	Guanidine Carbonate Added, % on Weight of Detergent Mixture	Detergency of 0.25% Solids Detergent, % Return to Original Reflectance	
			Wool	Cotton
Sodium propylene polymer toluene sulfonate	40	0	26	27
		5	69	35
Sodium propylene polymer benzene sulfonate	40	0	19	29
		5	71	35
Sodium keryl benzene sulfonate	40	0	20	—
		5	70	—
Sodium lauryl sulfate	60	0	61	33
		5	71	34
Soap (high titre)	100	0	90	—
		5	91	—
Straight chain non-ionic detergent	100	0	6	69
		5	15	70

* All detergent runs were made at 110°F. on wool and 130°F. on cotton (pH 10-11).

NITROGEN CHEMICALS DIGEST

In evaluating the effectiveness of guanidine carbonate for increasing the detergency of new products several concentrations based on the weight of detergent should be employed. The detergency data obtained should be plotted (see Figures 11 and 12) and the amount giving optimum detergency be ascertained from this graph.

The hard water tolerance of surface active agents is usually increased by adding guanidine salts (Table VI) (9).

TABLE VI
Effect of Guanidine Carbonate on Calcium Tolerance of a 0.25% Solution
of Sodium Alkylaryl Sulfonate

Guanidine Carbonate Added, % Based on Total Weight of Detergent Blend (40% active)	Calcium Tolerance* P.P.M. CaCO ₃
0	430
1	439
2	464
4	520
6	552
10	644
20	834

* The method of Hart (American Dyestuff Reporter, page 646, Nov. 19, 1934) was used.

TEXTILES

Guanidine derivatives are effective textile finishing agents having the added advantage that they do not discolor cloth. Many act as softening and wetting agents (58, 79, 90, 134, 135, 138, 139, 201, 220, 222, 224, 277, 310, 324, 379, 463), sizing agents (220, 352) and water repellents (2, 225, 310, 324). Guanidines are useful in many flame-retardant formulations (21, 119, 147, 150, 379). Guanidine phosphate provides a non-washfast fire resistance with no afterglow and no pronounced effect on the mechanical properties of the cellulosic material to which it is applied (9). The effectiveness of this material as a flame-proofing agent is demonstrated in Figure 13. Other guanidines, including guanidine-formaldehyde resins, give crease (122, 135, 139, 407) and fading (257) resistance, dye affinity (3, 56, 71, 122, 221, 225, 258, 278, 325, 374, 388, 476, 477) and increased tensile strength (57) to fabrics. Solutions of guanidine itself may be used as textile solvents (269, 283) and as saponification agents for cellulose esters (118, 223, 393).

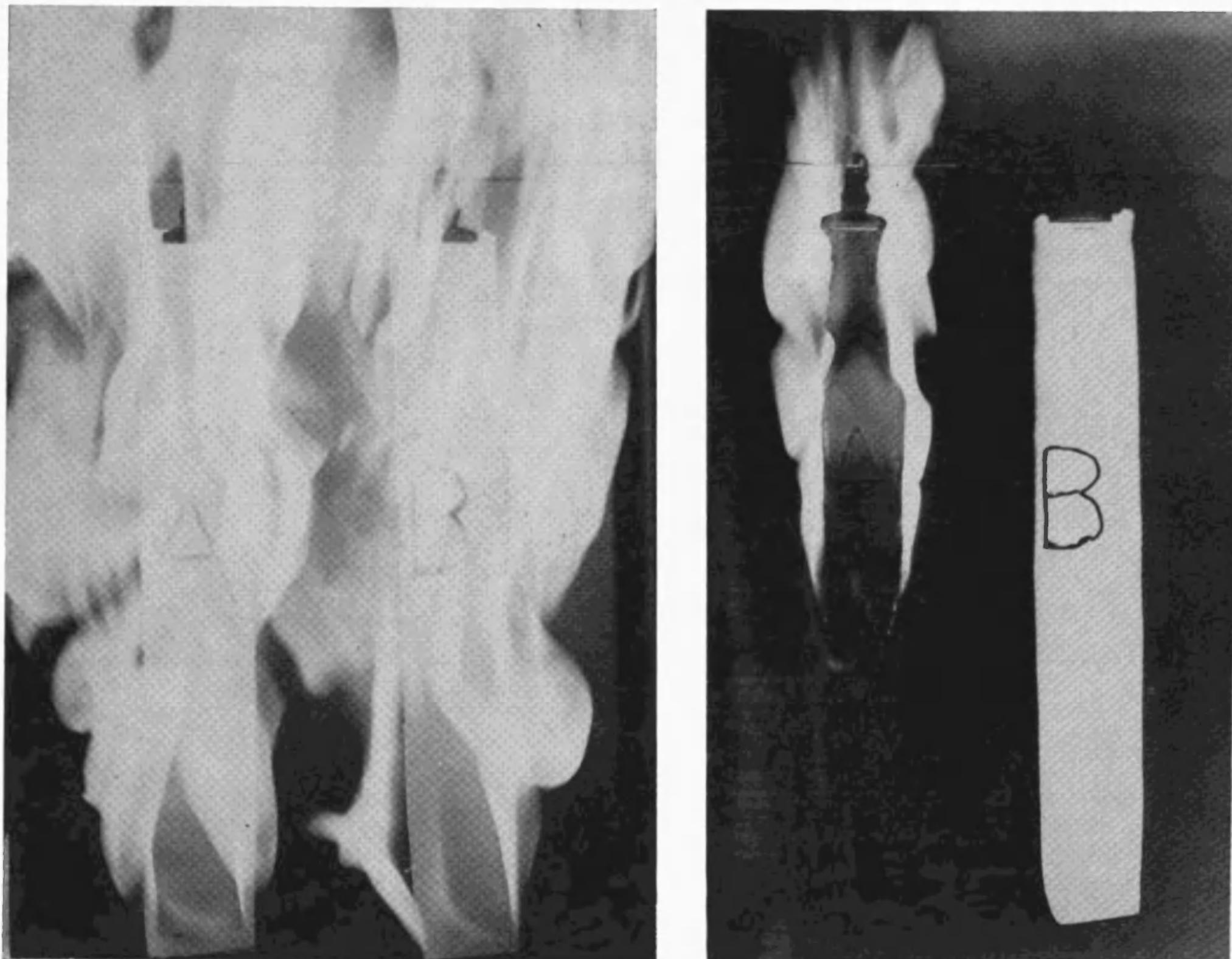


Figure 13—Guanidine Phosphate as Flame Retardant Agent

Two pieces of 5 oz. poplin cloth, one untreated (A) and one soaked in 15% guanidine phosphate solution, squeezed to obtain 100% wet pick-up, and dried (B), were wet with ethanol, suspended, and set afire. The picture on the left shows the ethanol ablaze. The picture on right, taken a few seconds later, after the ethanol had been burnt, shows the untreated cloth (A) burning while the treated cloth (B) has not been ignited

METHODS OF ANALYSIS FOR GUANIDINE

QUALITATIVE METHODS

Several schemes have been devised to detect the guanidine structure in the presence of other nitrogenous or carbamyl materials (64, 433). Some spot tests rely on colors formed when guanidines are treated with cupric or nickel sulfate (284), with sodium nitroprusside (444), with 1,2-naphthoquinone-4-sodium sulfonate (430), with alpha-thymol (145) or with pentacyanoferrate solutions (146). The last three methods are particularly useful. Other qualitative tests depend upon the formation of precipitates with benzenesulfonic acid (243) and with imidazole-4,5-dicarboxylic acid (339).

QUANTITATIVE METHODS

Guanidine is usually determined gravimetrically in the form of its nearly insoluble picrate (116, 465). The following procedure (9) is recommended for the analysis of guanidine carbonate, nitrate, sulfate, hydrochloride, monophosphate and diphosphate in the absence of interfering substances (see Notes 2 and 5 below):

Weigh out a sample, equivalent to 0.9 to 1.5 grams of guanidine picrate, into a tall-form 400 ml. beaker and dissolve in 10 ml. of water. Set the beaker into a large beaker of water, which is kept boiling on a small hot plate, and add from a dispensing burette, with continuous stirring, 250 ml. of 1.4 per cent ammonium picrate solution. The first 20 ml. of solution are added drop by drop and the remainder at a rate of about 70 ml. a minute. The final temperature of the solution reaches about 65°C. After all of the reagent has been added, remove the beaker from the hot water and immediately cool to 25°C. in a water bath. Allow the precipitated solution to stand at this temperature for 1 hour or longer with frequent stirring and then filter through a porous bottom or Gooch crucible. Wash the precipitate with about 50 ml. of freshly filtered 0.8 per cent ammonium picrate solution (saturated with guanidine picrate), taking care to remove the wash solution as completely as possible from the precipitate, dry for 2 hours at 105°C. and weigh as guanidine picrate. It is necessary to apply a correction for the solubility of guanidine picrate in the precipitating reagent and for the amount of wash solution left in the precipitate upon drying, etc. This combined correction is obtained from the correction curve (Fig. 14) and added to the amount of guanidine picrate weighed.

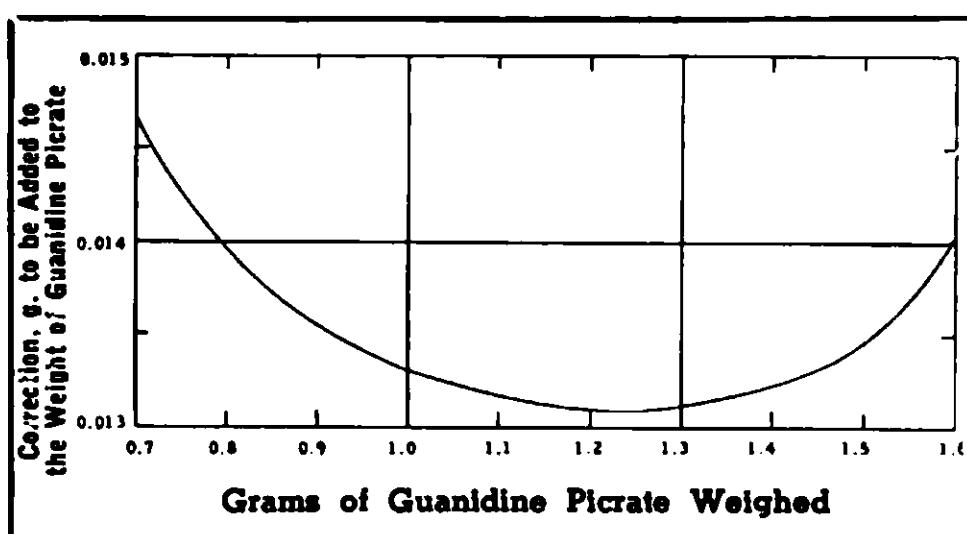


Figure 14—Guanidine Picrate Correction Curve

NOTES:

1. The correction curve was plotted from data obtained by precipitating various weighed amounts of guanidine hydrochloride, sulfate, nitrate and carbonate of known purity. Only one curve is necessary for analysis of the four guanidine salts, since the correction curves for the separate salts were found to be practically identical.

2. Picric acid (or ammonium picrate) is not a specific reagent for guanidine. Moreover, the solubility of guanidine picrate even in alkaline solutions is appreciable.

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3. Since guanidine carbonate is slowly hydrolyzed in water or dilute ammonia solution, certain precautions must be taken in its analysis. Do not allow a water solution of guanidine carbonate to stand any longer than necessary before precipitation. Add the precipitating reagent immediately after placing the beaker containing the sample in hot water.

4. It is important to adhere closely to the conditions established for the precipitation, i.e., warm solution and slow addition of precipitant. If a change is made, the extent of coprecipitation will probably change and this will necessitate the use of a different correction factor.

5. This procedure is suggested only for the determination of the guanidine content of the ordinary commercial guanidine salts, that is, samples containing only a small amount of ammonium salts as impurities. In the case of mixtures, the effect of other components must be ascertained.

Guanidine can also be determined gravimetrically as its nitranilate (312) or the methods of colorimetric (178, 289), nephelometric (373), or gasometric (459) analysis may be used.

QUANTITATIVE SEPARATIONS

Guanidine may be quantitatively separated from methyl guanidine by precipitation with beta-naphthylsulfonyl chloride (196), from amino acids by precipitation with 2,4-dinitrobenzoyl chloride (389) and from aminoguanidine by dissolution of the guanidine bicarbonate in sodium bicarbonate solution (438).

TOXICITY

At present there is little experimental data as to the toxicity of guanidine and its salts. However, Minot and her co-workers have administered *guanidine hydrochloride* to humans suffering from myasthenia gravis in daily doses of from 10-35 mg. per kg. without harmful effect (89, 304). They observed that gastrointestinal and other undesirable symptoms appeared when significant elevation of the blood level was persistently maintained, and that this could be relieved by atropine. The guanidine salt was administered either orally or intravenously.

Guanidine carbonate, which is rather strongly alkaline, may prove to be a skin irritant unless precautions common to the handling of alkalies are observed. Its alkalinity may be compared to that of sodium carbonate.

Preliminary experiments (9) indicate that 0.5% of *guanidine phosphate* in the diet of mice is not toxic and does not reduce food intake. No apparent irritation results when a 10% aqueous solution of the phosphate is applied on gauze to a rabbit's ear for one week.



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